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DISEASES OF THE THYROID GLAND

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CHAPTER I

STRUCTURE AND FUNCTION OF THE THYROID GLAND

(Brief Data)

The thyroid is situated on the anterior and lateral surfaces of the larynx and the trachea. It consists of two lateral lobes connected by an isthmus. The lateral lobes usually begin at the level of the sixth ring of the trachea and reach up to the middle of the thyroid cartilage, the isthmus is localised at the level of the first-fourth rings of the trachea. In half of the cases an additional lobe in the form of a pyramid stretches upward from the upper edge of the isthmus, from its right part. This pyramid can reach the level of the hyoid bone. The lateral lobes of the thyroid border on the trachea, partly on the larynx, oesophagus and the neck vessels; in adults they are from five to eight cm long, from two to four cm wide and from 1.2 to 2.5 cm thick.

The thyroid originates from an evagination of the ventral wall of the fore part of the intestinal tube between the first and the second pharyngeal pouches. A long thyroglossal duct (ductus thyreoglossus) develops from the pharyngeal cavity, divides dichotomically and becomes isolated from the pharynx. The lateral lobes of the thyroid, connected by an isthmus, are formed from the branches of this duct, while the pyramidal lobe emerging from the isthmus is the rudiment of the duct. Accessory thyroid

lobes may develop from the remnants of the duct. On the fourth month of embryonic life the thyroglossal duct becomes obliterated and a small depression (foramen coecum) remains at the basis of the tongue.

At the end of the first year of life the thyroid gland weighs one-two g. Up to the age of 20 it grows fast, particularly during pubescence and then continues to grow slowly until the age of 40-50 and in later years gradually shrinks. In the latter period dystrophic processes are seen in the parenchymal cells, the connective tissue proliferates and the blood vessels become sclerotic. In regions free from endemic goitre the thyroid gland in adults weighs approximately from 25 to 35 g. The weight and size of the thyroid gland of women are larger than that of men. It increases during each menstrual cycle and during pregnancy. Climatic conditions, the diet, intoxications, infections and other endogenous and exogenous factors affect the individual fluctuations in the weight of the gland.

The thyroid gland is covered with a fibrous capsule, strands of which invade the gland and produce lobulation; each lobule consists of separate minute alveoli or follicles, divided by connective tissue partitions. The walls of each follicle are lined with a single-layered epithelium, and the cavity is filled with a yellowish, viscid colloid. The follicles vary considerably in size, from 25 to 300 mu in transverse diameter.

At the beginning of its development the thyroid consists of solid cellular fibres, the follicles differentiate later and the thyroid goes through from the microfollicular to the more developed macrofollicular stage. The development of the thyroid gland and the differentiation of its follicular structure proceeds unequally among different people, depending on the environment, diet, the quantity of the salts entering the organism and the state of organ innervation.

Of special interest is the interfollicular epithelium consisting of single cells or cell groups—islets—which are

located in the thyroid between the mature follicles and come in close contact with them. In the islets, besides differentiated epithelial cells, there are symplastic formations with several nuclei located in the centre of the homogeneous protoplasmic mass. Many authors (P. V. Sipovsky, L. F. Larionov, T. I. Entin, Y. I. Glebina, et al.) took an interest in the role and significance of the interfollicular formations. Some of them regard the interfollicular epithelium as a cambial layer of undifferentiated embryonal cell elements, serving as a source for the proliferation of the epithelium during pathological growth of the parenchyma of the thyroid. Others consider it remnants of the follicular cells which degenerated at a definite stage of the secretory process.

B. V. Alyoshin, on the basis of his own conclusive study, regards the islet cells as a natural source for the replenishment and formation of parenchymal tissue of the thyroid gland throughout the life of the organism. In his opinion, the islet cells are formed from the cells of the follicular epithelium by amitotic division, they have the same functional properties as the epithelium of the follicles and, in view of this, can form into real follicles. According to this conception, the interfollicular islet epithelium is a product of the epithelium of mature follicles and a source for newly originating cells.

Lymphocytes in more or less large quantities, at times in considerable aggregates, are found in the fibrous base of the thyroid. Some authors (Williamson and Pearce, after N. Pende) attach special importance to the lymphoid tissue of the thyroid: the cells of this tissue, in their opinion, have a secretory property and produce a special iodine-free secretion, differing from the follicular secretion, which enters the lymphatic vessels of the thyroid. At present, when the functional connection between the thyroid and the adrenal cortex and the reaction of the latter to pathological changes in the former (which will be discussed later) are well known, and there are indica-

tions of a reverse dependence (Levitt) between the activity of the thyroid and the content of lymphocytes in it, the question of the lymphoid elements of the thyroid gland, insufficiently clear so far, demands special study.

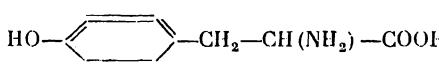
The thyroid is abundantly supplied with blood by the paired thyroid arteries, the superior and inferior, which arise from the external carotid and subclavian arteries respectively; more rarely is the blood supplied by the middle unpaired thyroid artery, which arises from the aortic arch. The arteries ramify over the surface of the gland, their branches enter into the thyroid structure forming a dense capillary network around each follicle. The exchange processes in the thyroid take place through the thin walls of the capillaries and the membranes of the follicle cells. The venous return of the blood from the thyroid goes through venules and veins into the jugular veins and the left innominate vein. The thyroid gland holds first place in the organism for the blood supply: the total mass of blood runs through the thyroid in one hour. Between the follicles there are small lymphatic vessels which go into the follicle cavities. The intercellular vessels gather into interfollicular, interlobular and interlobal vessels which produce a dense plexus on the surface of the thyroid and enter into the deep lymphatic vessels of the neck and pretracheal region (Matsunaga, after Pende).

The thyroid gland is innervated mainly by the superior, middle and inferior ganglia of the sympathetic trunk, the superior laryngeal, recurrent and cardial branches of the vagus and, according to M. Danelyan, by branches of the glossopharyngeal and hypoglossal nerves. The nerve branches enter deeply into the thyroid and produce a network of nerve fibres around each follicle, enter each follicle cell and end in the protoplasm of the cells in the form of buttons and lamellae and at the nucleus, in the form of brushes (Y. I. Tarakanov). The nerve elements of the thyroid regulate the tonus of the vessels and its secretory function.

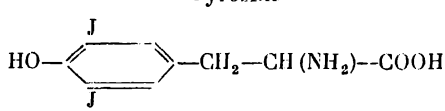
Experiments conducted by a number of Russian and

foreign authors with the object of ascertaining the connection between the thyroid and the vegetative nervous system have yielded contradictory results. According to data of B. V. Alyoshin, who in his experiments studied the reaction of the parenchyma of the thyroid *in vitro*, the addition to the medium of a sympathomimetic agent (adrenalin) resulted in greater tissue respiration, which pointed to its excitation, while the addition of a parasympathetic mediator (acetylcholine) inhibited the thyroid tissue.

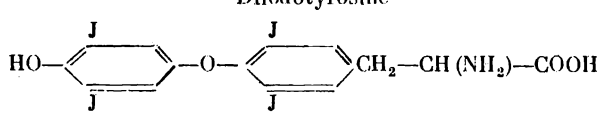
The function of the thyroid gland, as of every other endocrine organ, is manifested in the formation in it of a special chemical substance, a hormone, which is secreted directly into the blood stream. The hormone of the thyroid gland, thyroxin, has been known for a long time and has been well studied. It is a derivate of the amino acid tyrosine. It is formed from the fragments of two of its molecules in which four atoms of hydrogen have been replaced by iodine. Diiodotyrosine which possesses no hormonal properties is an intermediate product of the synthesis of thyroxin from tyrosine and iodine.



Tyrosine



Diiodotyrosine



Thyroxin

Thyroxin synthesised in the follicle cells constantly enters through the apical end of the cell into the follicular cavity where it is stored in the follicular colloid. From

there it is secreted through the basal part of the follicle cell into the capillary network. The structure of the thyroid makes it possible to judge its functional state. The inactive state is characterised by large follicles and a flat epithelium. They contain much dense colloid in their cavities. A functionally active thyroid is characterised by small follicles, fluid colloid and cylindrical follicular epithelium.

Thyroxin influences the degree of tissue oxygen consumption and cellular metabolism. Greater production of thyroxin increases the basal metabolic rate and a lower secretion of this hormone reduces that rate. Thyroxin stimulates the processes of protein deamination, elevates glycogenolytic and lipolytic processes in the liver, promotes the excretion of cholesterol from the body, accelerates the excretion of water by dehydrating the proteins and dilating the kidney vessels; chlorides, phosphates, calcium and other mineral substances are excreted with the water. The thyroid plays an especially important part in regulating iodine metabolism; changes in the function of the thyroid affect the content of iodine both in the thyroid itself and in the blood and also its excretion from the organism. Thyroxin regulates cardiovascular activity through the extracardial nerves and the neuromuscular apparatus of the heart itself. It also influences the digestive system and other functions of the organism.

The influence of the thyroid on the development of the growing organism has been demonstrated long ago. Direct proof of this has been furnished by the classical experiments accelerating the metamorphosis of tadpoles under the influence of thyroid tissue and thyroxin and by the clinical observations of retardation of the sexual, physical and mental development in patients with congenital hypoplasia and aplasia of the thyroid.

The thyroid and the thyroxin it produces exert an influence on the central nervous system and the functional state of its higher parts. The dependence of higher nerv-

ous activity of animals on the function of the thyroid gland has been conclusively demonstrated by the well-known experiments of A. V. Valkov with thyroidectomy of puppies and the experiments of M. K. Petrova with acute and chronic ingestion of thyroidin (desiccated thyroid) by dogs. Of particular interest in the investigations of Petrova is the different reaction of the animals of the strong and weak type of higher nervous activity to the same doses of the thyroid hormone.

The influence of thyroidectomy, of small and large doses of thyroidin on higher nervous activity has also been studied by a number of other authors (D. M. Zavadovsky and A. L. Zak; M. A. Usiyevich, Y. I. Artemyev, T. T. Alexeyev, and A. D. Stepanova, G. N. Pribytkova and others). V. G. Baranov, Y. N. Speranskaya and D. S. Tendler have demonstrated in their experiments on dogs that the prolonged administration of thyroidin causes deep alterations of higher nervous activity, particularly among animals of the weak type, in the very first days of the ingestion of the preparation in such small doses which throughout the duration of the experiment exert no influence either on the weight of the animals or the degree of tissue oxygen consumption.

Of the structural changes in the central nervous system under the influence of thyroidectomy and hyperthyroidisation described by a number of authors (V. Avtokratov, B. N. Mogilnitsky, D. I. Fridberg) the observations of A. Y. Rabkina are of great interest. Inhibiting the function of the thyroid by methylthiouracil, she observed histological alterations in various parts of the cerebrum, similar to those after thyroidectomy. She succeeded in preventing these alterations by the simultaneous administration of a definite dose of thyroidin. A doubling of this dose, however, caused morphological alterations in the central nervous system different from those induced by methylthiouracil and evidently determined by the excessive dose of the preparation. Thus, in conditions of the same experi-

ment a morphological reaction of the central nervous system was established both to the insufficient and excessive content of the thyroid hormone in the organism.

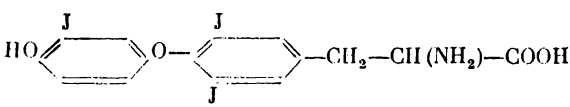
The thyroid gland, for its part, is subject to the constant regulatory influence of the central nervous system and its higher parts. This is indicated by experimental studies of R. P. Olnyanskaya, I. A. Eskin, Y. B. Skebelskaya, M. S. Kakhan, B. V. Alyoshin, A. A. Voitkevich and others and also by data of clinists (V. G. Baranov, N. A. Shereshevsky, M. A. Kopelovich and our observations) which testify to the exceptional role of the psychic trauma in the genesis of thyrotoxicosis. The influence of the central nervous system on the thyroid is effected through the nerve conductors by means of intricate nerve reflectory reactions, bypassing the hypophysis, and through the anterior lobe of the hypophysis by means of the thyrotropic hormone secreted by the basophil cells of the hypophysis. This hormone has now been obtained in a relatively pure state.

The thyrotropic function of the hypophysis has been studied in detail by Russian investigators (B. V. Alyoshin, Y. M. Kabak, A. A. Voitkevich, P. A. Vunder, Y. B. Skebelskaya and others). Alyoshin has presented a harmonious picture of the interaction of the thyrotropic hormone of the hypophysis and the thyroid. The thyrotropic hormone not only stimulates the follicular epithelial cells to produce the thyroid hormone which enters through their apical end into the follicular cavity, but also consecutively activates the processes of hydrolysis of the intrafollicular colloid and also the reabsorption by the follicular cells of the products of hydrolysis and the excretion of the latter through the basal part of the cells into the capillaries surrounding the follicles. According to Alyoshin's conception, greater production of the thyroid hormone by the interfollicular islets, under the influence of the thyrotropic hormone, stimulates the conversion of the islets into microfollicles. In this way the hypophysis

exercises simultaneous control over both the function and the structure of the thyroid which are thus interconnected.

As for the point of application of the thyrotropic hormone in the thyroid gland itself, Alyoshin objects to the opinion of S. M. Leites that it is the neuroreceptors of the thyroid. On the basis of data obtained in experiments with the reaction of an isolated thyroid gland to the thyrotropic hormone, Alyoshin holds that the hormone of the hypophysis acts directly on the epithelial cells of the follicles by activating their fermentative systems. But he does not take into account the fact that the conditions of reactivity in a whole organism are entirely different from those in an isolated organ. P. A. Vunder in experiments arranged to study the conditioned reflex reaction to the introduction of the thyrotropic hormone has shown that in a whole organism the thyrotropic hormone acts through the central nervous system.

In 1950 an iodine compound, 3, 5, 3-triiodothyronine, was found by Gross and Pitt-Rivers in the thyroid and in the blood plasma in 1951. Subsequently it was also obtained synthetically.



3, 5, 3-Triiodothyronine

This compound is saturated with iodine more than diiodotyrosine and 6.1 per cent less than thyroxin. Its content in the thyroid is only 1/15-1/20 of thyroxin, but it acts much faster and its activity, according to various authors, is from 4 to 10 times greater than the activity of thyroxin. As compared with thyroxin, triiodothyronine in a much smaller dose elevates tissue oxygen consumption, reduces the uptake of radioactive iodine by the thyroid and the content of cholesterol in the blood, nullifies the goitrogenous action of thiouracil, prevents the retardation of growth and development of myxoedema after thyroidectomy. It is

important to note that even in peroral administration triiodothyronine preserves an activity twice greater than thyroxin.

The way triiodothyronine is formed in the organism remains an unsolved question so far. The assumption that it originates from thyroxin deiodised in the periphery has little grounds when comparing the biological action of these two hormones in point of time. It is more correct to assume that the synthesis of triiodothyronine, like that of thyroxin, takes place in the thyroid itself from mono- and diiodotyrosine (Roche, Lissitzky and Michel), but so far it has not been obtained synthetically from these two components.

CHAPTER II

THYROTOXICOSIS

Pathogenesis and Aetiology

A special syndrome, which included separate symptoms of thyrotoxicosis, enlargement of the thyroid among them, was described by a number of authors (Morgagni, Parry, Graves, Basedow) between 1761 and 1843. But it was only in 1886 that Möbius for the first time pointed to the pathogenic role of the thyroid gland in the development of this syndrome. Since then wide currency has been gained by the view that the thyrotoxic symptom complex, supplemented as a result of further observations, pathogenically is determined solely by the influence exerted on various organs and tissues by thyroxin excessively produced in the hyperplastic thyroid.

This opinion has been confirmed by the complete or partial remission of thyrotoxicosis or the noticeable mollification of the thyrotoxic symptoms after thyroidectomy among a considerable number of patients, and also by the possibility of the appearance of these symptoms when preparations of the thyroid gland are introduced experimentally or in case of their abuse in clinical treatment.

Möbius, however, held that in thyrotoxicosis, in addition to the usual excessively produced thyroxin hormone, a toxic substance qualitatively different from thyroxin is secreted by the thyroid and enters the body and that its action determines the development of the disease. Ac-

cording to M. R. Weber, this view was also shared by Klose, Askanasy and Lubarsch. Plummer thought that it was a case of thyroxin insufficiently saturated with iodine. The opinions voiced concerning a special incretion produced by the thyroid in thyrotoxicosis are little convincing and are of an abstract nature, inasmuch as not one of the above-named authors has succeeded in isolating that substance. Triiodothyronine, obtained in 1950, is more active than thyroxin, but it is a usual product of the vital activity of the thyroid produced by it in physiological conditions as well. There are no grounds whatsoever for considering that the correlation between these two incretions of the thyroid changes quantitatively in thyrotoxicosis.

Supporters of the hypothyroidal genesis of thyrotoxicosis (Walter, Notkin, Blum, after Weber) assumed that the deficiency in the organism of the thyroid hormone deranges the main function of the gland—detoxication of the endotoxins of protein origin formed in the organism—and that thyrotoxicosis develops in the organism as a consequence of the action of these endotoxins. On the basis of the antitoxic conception of the role of the thyroid in the organism, at one time a preparation made from a serum of thyroidectomised animals was used widely for the treatment of thyrotoxicosis with the aim of binding the excess quantities of thyroxin by the endotoxins contained in the preparation. The hypothyroidal theory of the genesis of thyrotoxicosis is also inacceptable because it effaces the border line between the genesis of thyrotoxicosis and myxoedema, the clinical picture of which is directly opposite, not to mention the fact that so far no special endotoxins have been discovered by anyone either in the hyperfunction or hypofunction of the thyroid.

The different interpretation of the role of the thyroid in the genesis of thyrotoxicosis is due to the fact that the further study of the problem has shown that the hyperfunction of the thyroid alone cannot explain a number of phenomena observed during the development and

course of thyrotoxicosis. Thus, no explanation has been furnished for the exceptional role of the psychic trauma in the aetiology of this disease, the non-conformity between the degree of pronounced clinical symptoms and the size of the thyroid, for the phenomena of thyrotoxicosis remaining after subtotal thyroidectomy among some patients or arising anew after a certain period following the operation even when there was no relapse of the goitre and most often after some emotional strain.

Nor has an answer to this question been supplied by the muscular-peripheral theory of Zondek, according to which the excess production of thyroxin by the thyroid and the increase, under its influence, of oxidative processes in the tissues is only a responsive reaction to local primary alterations in the electrolytic system causing the loss of the capacity for the normal assimilation of oxygen by muscle tissue. The ionic correlation and the metabolic processes in the cell undoubtedly play a part in the reactivity of the cell to the nerve impulses it receives. Disturbances of intercellular metabolism is only one of the links in the chain of the complicated pathological process, but they cannot determine it fully.

What makes these and similar theories insolvent is that, rightly stressing the role of the thyroid in the pathogenesis of thyrotoxicosis (without the hyperfunction of the thyroid there is no thyrotoxicosis), they at the same time do not take into consideration the role of the central nervous system, of its higher parts, in the regulation of vital processes and its participation in the developing pathological process. Even when the authors of these theories sought for an explanation of some symptoms of thyrotoxicosis in the nervous system, they referred only to the vegetative system, moreover, as fully subordinated in its manifestations to the thyroxin which acts humorally upon it.

But, according to modern conceptions, one section of the nervous system must not be functionally separated

from another. An indivisible nervous system headed by its higher parts ensures in the entire organism the speed of its reactions to the constantly changing factors of the internal and external environment necessary for the organism's normal existence. Any derangement or breakdown of higher nervous activity under the influence of external and internal irritants which are unusual or excessive for their intensity and length, disturb the functions of peripheral organs; the ones to suffer first are those whose nerve receptors are capable of responding, by elevated or decreased reaction, to the abnormal impulses coming from the centre.

From this viewpoint the pathogenesis of thyrotoxicosis can be pictured as follows. Under the influence of an external or internal pathogenic agent a pathological focus of excitation or inhibition is created in the cerebral cortex. In their turn, these focci maintain a pathological focus of excitation in the subcortical centres, the first through irradiation and the second through positive induction. The pathological focus, acting through the efferent nerve paths, given a definite reactivity of the nervous apparatus of the thyroid, intensifies its function and causes increased production of thyroxin. The thyroid can also be influenced in the same direction by the hypophysis, whose hormonal activity is likewise elevated under the influence of cerebral pathological impulses. The excess quantity of thyroxin circulating in the blood when the function of the thyroid is intensified, in its turn, maintains and increases the pathological condition of the higher parts of the central nervous system. Thus, a pathological process which arises as a consequence of the abnormal activity of the central nervous system becomes intensive and stable and gains definite clinical outlines.

Primary alterations of the thyroid can also lead to thyrotoxicosis, true, less frequently. Any inflammatory process, including suppurative ones (thyroiditis and strumitis), any structural changes of the thyroid in endemic goitre

can raise the sensitivity of its neuroreceptors to usual irritants and lead to hyperfunction of the thyroid, with the subsequent involvement of the higher parts of the central nervous system in the process, and the development of a full picture of thyrotoxicosis.

It follows from the aforesaid that the pathogenesis of thyrotoxicosis is complicated. It consists of two components—the nervous and thyroidal, whose interconnection maintains the pathological thyrotoxic process.

D. I. Fridberg attaches special significance to a number of additional factors in the development of thyrotoxicosis. Among them are: 1) hypoxia of tissues observed in thyrotoxicosis; it is caused, on the one hand, by the limited supply of oxygen owing to tissue oedema as a consequence of increased permeability of the blood vessels and, on the other, by the lower capacity of the cells to utilise oxygen; 2) the appearance of toxic substances as a result of disturbance of the detoxicating function of the liver; 3) hypovitaminosis B_1 and C which takes place in thyrotoxicosis. All these factors, in the opinion of Fridberg, especially affect the condition of the central nervous system, particularly the motor elements of the cerebrum and spinal cord. The deficiency of vitamin B_1 affects the transmission of excitation in the synapses owing to the insufficient formation of acetylcholine. Objections may be raised to the exceptional role Fridberg ascribes to these factors in the genesis and development of thyrotoxicosis, but the possibility of their adverse influence, as additional agents, on the course of the thyrotoxic process is not precluded.

It is also necessary to examine the pathomorphology of the thyroid and its nerve elements. The patho-anatomical picture observed when examining the thyroid differs, depending on the duration and severity of the thyrotoxicosis. We shall deal with the state of the thyroid in cases of severe thyrotoxicosis or moderately severe forms not curable by conservative means when patients are usually

operated upon and the resected thyroid is therefore available for histological study. But even in such cases the complete picture of the changes in the thyroid is obscured by earlier antithyroid therapy (in some cases over a long period). It is also necessary to make the reservation that we refer to a primary thyrotoxic goitre and not to an euthyroid endemic goitre with secondary thyrotoxicosis.

In case of a primary thyrotoxic goitre the thyroid gland is diffusely enlarged, not only on account of its parenchymatous elements, but also the substantial expansion of its entire vascular system. The follicles are of different size and form, with papillary-like extensions and pillow-like prominences (Sanderson's pillows). Cell proliferation at times fills the entire follicle, covering its lumen, whereas the interfollicular cellular proliferation is the initial material for forming new follicles. The follicle has a single-layered epithelium, more seldom a stratified epithelium of cubical or columnar form. The lumen of the follicle contains a small amount of colloid of a faintly pinkish colour. The colloid adheres to the wall or appears completely vacuolated. Some follicles have no colloid. The connective tissue in a primary thyrotoxic goitre is poorly developed. Its proliferation and subsequent sclerotic changes resulting in cirrhosis are noted only in prolonged thyrotoxicosis as a reaction to the degenerative processes in the parenchymatous tissue of the gland.

Thyrotoxicosis also affects the nervous elements of the thyroid. According to data of Y. I. Tarakanov, one observes in the nerve fibres and fibrils pear-shaped and spherical swelling (phenomena of irritation), fragmentation and partial disintegration (degeneration phenomena), and growth, which precedes proliferation of the follicular epithelium, with the eventual formation of "end nevroms" (regeneration phenomena). In thyrotoxicosis, accumulations of small lymphoid cells in the form of lymph nodes are found more often in the interfollicular connective tissue, and less frequently in the parenchyma of the thyroid.

According to data of various authors, they are found in from 70 to 90 per cent of the patients. In the opinion of Wahlberg, they represent a local reaction to the greater secretory activity of the hyperplastic epithelial tissue. According to other authors, the lymphoidal infiltration of the thyroid in thyrotoxicosis is a local compensating factor. Cells of the lymphoidal type possess phagocytic ability in relation of epithelial cells (Glormaghtigh, after Weber) or by their proliferation prevent the development of the epithelial cells (T. Levitt) and the production of thyroxin by them. Observations of the functional state of the adrenals made in cases of thyrotoxicosis furnish a basis for evaluating in a different way the hyperplasia of the lymphoid tissue in the thyroid. In this sense it is a part of the general lymphocytaric reaction of the organism and is an indicator of the functional exhaustion of the adrenal cortex in severe and prolonged thyrotoxicosis; it is a signal not of mobilisation, but of the weakening of the organism's defensive forces in the struggle against thyrotoxicosis.

The significance of the most frequent factors in the aetiology of thyrotoxicosis is fully in line with the contemporary views of the pathogenesis of this disease. Psychic trauma holds first place among them. As far back as 1884, S. P. Botkin wrote: "The influence of psychic factors not only on the course but also on the development of Basedow's disease is beyond all doubt. This circumstance gives me as a clinician the right to look upon Basedow's disease as an ailment of cerebral origin." V. D. Shervinsky writes: "A shock of the nervous system plays a tremendous part and is the predominating, perhaps, the biggest link in the chain of causes of Basedow's disease." According to data of N. A. Shereshevsky, the proportion of psychic traumas in the aetiology of thyrotoxicosis reaches 80 per cent. According to our data, this percentage is somewhat smaller, but is still considerable and greatly exceeds for its frequency all the other aetiological moments. The death or grave illness of relatives, fright, fear, con-

flicts and prolonged excessive overstrain figure most often among the psychic traumas which cause thyrotoxicosis. The degree of reaction to the psychic trauma is not always adequate to the gravity of the actual situation; evidently the individual moment, i. e., the state of the nervous system prior to the psychic trauma, plays an exceedingly big part here.

If we analyse all the enumerated types of psychic traumas leading to thyrotoxicosis, all of them resolve to sharp and chronic nervous irritants which cause a pathological state of the higher parts of the central nervous system either by their unusual nature or excessive power and duration of action. Consequently, these are categories of irritants which in the experiments of I. P. Pavlov and his collaborators induced neuroses in dogs, owing to overstrain of the excitatory or inhibitory process in the cortex, with a breakdown of normal higher nervous activity.

Infections hold the second place for frequency in the aetiology of thyrotoxicosis. According to our data, they are the cause of thyrotoxicosis among 17 per cent of the patients. It is usually held that the infective matter and its toxins circulating in the blood by their direct action on the thyroid cause greater secretion of thyroxin and thyrotoxicosis as a direct reaction of various organs to the excessive thyroid hormone circulating in the blood. But such a conception does not conform to the contemporary view about the development of the pathological process and runs counter to clinical observations. Thyroiditis and strumitis, under which a severe infectious process takes place in the thyroid gland itself, frequently regress without a subsequent disturbance in the function of the thyroid gland. Similarly, syphilitic lesion of the thyroid seldom leads to thyrotoxicosis. The view that infection can influence the development of thyrotoxicosis only in this way is also refuted by the fact that thyrotoxicosis can arise after various infections (streptococcal, bacillary, viral, intestinal and parasitic).

Taking into account the leading role of the central nervous system in all vital processes of an organism both in a normal and pathological state and also the cerebral phenomena observed in any infection which frequently even precede other pathogenic symptoms, we may assume that infection, besides the direct effect on the thyroid gland, may cause functional changes in the central nervous system by its infective matter and pathological products of metabolism which arise in the course of the infectious process, and this, as pointed out earlier, may lead to thyrotoxic phenomena.

Influenza and angina are the most frequent infections which cause thyrotoxicosis. According to our observations, influenza and angina account for 36 to 40 per cent of the thyrotoxicosis caused by infections. Thyrotoxicosis may also develop in connection with other infections, such as malaria, erysipelas, scarlet fever, typhoid fever, etc.

Some authors stress the importance of acute and chronic tonsillitis in the development and maintenance of thyrotoxicosis, especially in children. In a combination of thyrotoxicosis and tonsillitis it is difficult, and at times almost impossible, to establish anamnestically which of these pathological conditions preceded the other as an aetiological factor, but the considerable frequency of such combinations offers reasons for the assumption that they are interconnected and interact pathogenically. A study of materials of the All-Union Institute of Experimental Endocrinology for a period of 18 years covering 1,281 patients made by N. A. Preobrazhensky, an otolaryngologist, showed that 34.5 per cent of the patients had a combination of thyrotoxicosis and tonsillitis. In all these patients the simultaneous treatment of tonsillitis by all the generally accepted means was an indispensable condition for the successful cure of thyrotoxicosis. If a patient, owing to the severity of thyrotoxicosis, has to be operated on, this should be preceded by treatment of

tonsillitis. Like other authors, we have observed that active treatment of tonsillitis favourably affects the course of thyrotoxicosis. The apprehensions of some otolaryngologists about treating tonsillitis before thyrotoxicosis is cured or mollified are utterly groundless.

The aetiological significance of chronic infections, tuberculosis and syphilis, in the development of thyrotoxicosis should be discussed separately.

Tubercular lesion of the thyroid is seldom observed, but tuberculosis of any localisation might, as any other infection, affect the development of thyrotoxicosis. Ch. Maslinsky infected white mice with tuberculosis by an intravenous injection of 0.2 mg of a suspension of tubercular bacilli and observed tubercular lesion of the lungs and a picture of thyroid hyperfunction, but without tubercular infection of the gland itself. In the clinic thyrotoxicosis, according to some authors, is found among 15 per cent of the patients with tuberculosis of the lungs, and an enlargement of thyroid without disturbance of its function, among 18 per cent. A combination of an enlarged thyroid with tuberculosis of the lungs in one or another degree of activity has been found much more frequently. To reveal clinically in such a combination the hyperfunction of the thyroid is not so easy since tubercular intoxication in the main yields the same symptom complex as thyrotoxicosis (tachycardia, weight loss, perspiration, subfebrile temperature, muscular fatigue, elevation of the basal metabolic rate, etc.). Special symptoms of one or the other disease (for example, chill and big fluctuations of temperature in tuberculosis, eye symptoms and tremor in thyrotoxicosis) are inconstant and do not preclude the coexistence of both diseases. Such combinations are sometimes called thyro-tuberculosis. This term means not a tubercular lesion of the thyroid gland, but such a state when the clinical picture can with equal grounds be credited both to active tuberculosis of the lungs and to thyrotoxicosis. Radioiodine diagnostics can to a certain

extent (but not absolutely) help ascertain the degree of participation of the thyroid in the pathological process.

The question arises of the tactics to be followed by the doctor when faced with a combination of the two diseases. The existing opinion that the hyperfunction of the thyroid gland in tuberculosis is of defensive importance for the organism and that consequently it is inadvisable to combat thyrotoxicosis is insufficiently substantiated. According to data of Ch. Maslinsky, tubercular lesions of lungs in experimental tuberculosis was also observed in mice which had preliminarily been given preparations of the thyroid gland for a long time. Evidently those who support the view that thyrotoxicosis has an adverse effect on the course of the tubercular process and on the organism as a whole are more correct. And this is understandable. The organism suffers doubly from a combination of tuberculosis and thyrotoxicosis. Both the tubercular and thyroidal intoxications affect the nervous system and metabolic processes in the one and the same direction (that is why the symptomatology of both diseases is similar in many respects). This dual blow at the organism demands struggle on two fronts—antituberculosis measures must be combined with antithyrotoxic medication.

In the case of a combination of thyrotoxicosis and tuberculosis methylthiouracil is ruled out because it is contraindicated for active tuberculosis, but the use of microdoses of iodine may be considered (the use of both preparations in treating thyrotoxicosis will be discussed later). Here the endocrinologist often encounters objections of the phthisiotherapist who is afraid to use iodine therapy because of the ability of iodine to cause lung haemorrhage. In this connection it should he recalled that many authoritative phthisiotherapists (Noël, Lépine, Stücker, Landouzy) of the end of the 19th century and the beginning of the 20th century observed good results in the treatment of tuberculosis of the lungs (acute and fibrous forms) with

iodine tincture (20 drops daily) and potassium iodide (1.5 g daily). While treatment with large doses of iodine is fraught with the danger of provoking a lung haemorrhage, microdoses of iodine (one mg of pure iodine and 10 mg of potassium iodide per dose, twice daily) can be used for treating thyrotoxicosis in any form of tuberculosis without any risk, the more so when there is no inclination to haemoptysis. If the nature and severity of thyrotoxicosis demands an operation, it is not contraindicated. This question must be co-ordinated with the phthisiotherapist because here it is necessary to reckon with the state of the process in the lungs before the operation and possible postoperative lung complications.

Syphilitic lesion of the thyroid is not such a rare phenomenon and is met frequently in case of acquired syphilis. A thyroid affected by syphilis is firm and not quite mobile because it is inosculated with surrounding tissues. But in contrast to cancer of the thyroid the condition of the patient is satisfactory and no cachexia is observed. In syphilis of the thyroid its hyperfunction, as pointed out earlier, is observed only in some patients. This is explained evidently by the predominantly destructive nature of the syphilitic process in the thyroid. Thyrotoxicosis in such cases can sooner arise in the neurohumoral way when the syphilitic process is localised on some other organ.

The special symptomatology (bradycardia, eosinophilia and the absence of tremor), ascribed by some authors (V. M. Kogan-Yasny, Schulmann) to thyrotoxicosis of syphilitic origin, is theoretically not substantiated and clinically not justified. The syphilitic genesis of thyrotoxicosis can be assumed not on the basis of alleged special symptoms inherent in it, and not of distinctions of the syphilitically affected thyroid, which are not determined reliably by palpation, but only by anamnestic and serological data confirming that the syphilitic infection preceded thyrotoxicosis.

Thyrotoxicosis develops not infrequently against the background of some other endocrinal pathology that preceded it. Formerly such thyrotoxicosis was regarded from the narrow positions of synergism and antagonism between separate glands, closed and isolated from the entire organism by the framework of the endocrinal system. At present the onset of thyrotoxicosis against the background of other endocrinal disturbances should be assessed in a different way. As pointed out earlier, a change in the functions of one or another endocrinal gland undoubtedly reflects on the normal functions of the higher parts of the central nervous system and the organs and glands connected with them, which in certain conditions may lead to hyperfunction of the thyroid.

Thyrotoxicosis often arises in disorders of the hypophysis (acromegaly, Itsenko-Cushing's disease) since the hypophysis is anatomically and functionally closely connected with the central nervous system and through thyrotropin, with the thyroid gland. Disturbance of the function of the hypophysis might affect the activity of the thyroid both neurogenally and humourally.

Thyrotoxicosis is observed in congenital and acquired sex hormone deficiency (eunuchoidism, castration). Derangement of higher nervous activity as a result of castration was conclusively demonstrated experimentally by Pavlov and M. K. Petrova. Thyrotoxicosis in case of sex hormone deficiency might be the result of disturbance of the normal connections between the central nervous system and the thyroid gland.

Thyrotoxicosis often observed in the pubescent and climacteric periods and pregnancy among women is of special interest. The modern conception of neuro-endocrinal relations makes it possible to give a fully substantiated interpretation of this form of thyrotoxicosis. The sex hormone, like other hormones, according to the studies of Pavlov and his associates, is a strong, constantly acting endogenic irritant of the cerebral cortex and, to-

gether with other endogenic and exogenic irritants, participates in shaping and maintaining the dynamic stereotype of higher nervous activity. The inclusion of the sex hormone in the pubescent period and its exclusion in the climacteric period lead to changes in the dynamic stereotype of the higher nervous activity and this, according to Pavlov and the data obtained by Petrova in experiments with castrated dogs, places an excessive load on the central nervous system. As a result, there arises a reaction of the type of a general neurosis and when the thyroid is drawn into the process, a reaction of the type of thyrotoxicosis. This conception is fully in line with clinical data which show that thyrotoxicosis is observed clinically in the climacteric and pubescent periods and during pregnancy only at times, while neuroses of varying degree almost always occur in these periods.

Clinical Picture

A diffuse, usually equal enlargement of the thyroid occurs in primary thyrotoxicosis. Its soft consistency differs from the more or less dense consistency of an endemic goitre with frequently palpable nodules running in size from a bean to a big apple. The enlargement of the thyroid is a characteristic, but not the earliest, symptom of thyrotoxicosis, since the hyperfunction of the thyroid which determines in the main the thyrotoxic syndrome precedes its hyperplasia. This circumstance makes it harder to diagnose the initial forms of thyrotoxicosis which are often overlooked and, because of similar symptoms, are taken to be ordinary neuroses.

The thyroid is enlarged either swiftly, reaching a definite size preserved throughout the duration of the disease, or slowly; at times in the course of the disease its size changes, growing either smaller or larger. No conformity between the size of the gland and the severity of thyrotoxicosis has been established, inasmuch as the

manifestation of thyrotoxic phenomena depends not only on the degree of hyperplasia and the hyperfunction of the thyroid, but also on the reaction of the organism to the excessive thyroxin produced. Frequent fluctuations in the size of the gland may depend on the degree of the blood volume. In case of strong vascularisation of the thyroid its distended vessels protrude on the surface. Their pulsation can frequently be seen and the vascular bruit can be heard when pressing with the stethoscope (owing to high pulse pressure in thyrotoxicosis); at times it is possible to see the rhythmical shifting of the gland up and down as a result of the pulsation of the carotid arteries and sometimes of the jugular veins.

There are five degrees of thyroid enlargement: I degree—the gland is palpable, especially its isthmus, but the enlargement is not noticeable to the eye; II degree—the gland is well palpable and its enlargement is noticeable when the patient swallows; III degree (Fig. 1)—the gland is well seen without swallowing; IV degree (Fig. 2)—the gland is substantially enlarged; V degree (Fig. 3)—the gland is very large.

Fig. 1. Patient, age 16, with severe thyrotoxicosis. Diffuse enlargement of the thyroid III degree. Pronounced eye symptoms.

The enlarged thyroid is palpable on the anterior and lateral surfaces of the neck, inwardly of the sternocleidomastoid muscles. When the lateral lobes are of large size they push the sternocleidomastoid muscles far outward and forward. But palpation data alone are insufficient for judgement about the size of the thyroid because it can be fully or partly located behind the sternum.

Fig. 2. Patient, age 31, with severe thyrotoxicosis. Diffuse enlargement of the thyroid IV degree.

Fig. 3. Patient, age 36, with severe thyrotoxicosis. Diffuse enlargement of the thyroid V degree.

In such cases only roentgenoscopy can help locate the thyroid gland and give an approximate idea of its size; for a more exact idea roentgenography is needed. But even data of a roentgenological study can prove delusive if the gland is located circularly around the trachea and oesophagus. Divergences between the expected size of the gland, judging from palpation and roentgenological data, and its actual size, established during an operation, is not such a rare phenomenon.

Cardiovascular alterations are the most important symptom of thyrotoxicosis for frequency and significance. Frequent contractions of the heart and its more intensive work, which arise already in the early stage of the disease, lead subsequently to hypertrophy of the heart (functional hypertrophy) and then to its enlargement, which might cause distension of the atrioventricular ring and, as a con-

sequence of this, relative insufficiency of the mitral valve. Hence tachycardia, a rise of systolic blood pressure, resistant diffuse apex impulse, extension of the heart boundary to the left, systolic murmur in the apex and in the third left intercostal space near the sternal margin are observed. One can often hear functional murmurs in the pulmonary artery (in the second intercostal space of the sternal margin). Together with the more forceful contractions of the heart, the tonus of the peripheral vessels drops reflexly and pressure in them is lowered, as a result of which arterial pressure in thyrotoxicosis is characterised by high pulse pressure (with a relatively high systolic pressure and a relatively low diastolic pressure). More intensive cardiovascular activity in thyrotoxicosis is accompanied, moreover, by an increase in systolic and minute cardiac output, an increase in volume of circulating blood and the rate of circulation.

The enumerated haemodynamic shifts in a more or less pronounced degree take place in each patient, but alterations of the heart rhythm might not be observed altogether or take the form of sinus (so-called respiratory) arrhythmia and more rarely of extrasystoly. But in severe forms of thyrotoxicosis auricular fibrillation is not so rare. According to data of Russian authors, it reaches up to 10 per cent, and of foreign authors, up to 20 per cent. There is a viewpoint which denies the purely thyrotoxic origin of auricular fibrillation and considers that it can occur only in a combination of thyrotoxicosis and cardiovascular ailments (coronary sclerosis, stenosis of the mitral valve) which by themselves cause auricular fibrillation, while thyrotoxicosis plays only the part of an additional factor. But most Soviet authors (L. Y. Siterman, A. P. Preobrazhensky and M. S. Turkeltaub, Y. S. Dræchinskaya, and M. P. Andreyeva, G. F. Lang and others), on the basis of a substantial number of clinical observations, hold that severe thyrotoxicosis can be complicated by

auricular fibrillation even if there are no cardiovascular lesions. We adhere to a similar view.

Severe thyrotoxicosis of long duration furnishes sufficient prerequisites for the development of auricular fibrillation. It causes deep dystrophic and frequently degenerative alterations in the myocardium, which works with a great strain under the high intensity of metabolic processes in it. The excitability of its weakest section of the atrium to extracardial impulses is lowered, heterotypic impulses of varying frequency arise in the atriums and they spread in different directions; contractions of the ventricles, irregular for their force and rate of beat, arise in case of definite changes in the excitability and conductivity of the atrioventricular node and the bundle of His. The persistence and degree of auricular fibrillation depend on the nature and depth of lesion of the atriums and the intercardial conductive system. In case of severe lesion of the tissues of the atriums auricular fibrillation might persist even after the cure, notwithstanding the mollification of other thyrotoxic phenomena. If, however, functional disturbances prevail, auricular fibrillation disappears, together with other thyrotoxic symptoms, under the influence of effective treatment of thyrotoxicosis. Consequently, auricular fibrillation does not speak of irreversible processes in the myocardium, but particularly in tachycardia and great pulse deficiency it is an additional factor which sharply lowers the working capacity of the cardiovascular system affected by thyrotoxicosis, contributing to its premature insufficiency. That is why in thyrotoxicosis auricular fibrillation is a grave signal indicating the need for urgent radical measures.

Auricular fibrillation which arises in the process of dynamic observation of the patient against the background of preceding thyrotoxicosis, with the progressive increase of thyrotoxic phenomena, confirms its thyrotoxic genesis. But the presence of auricular fibrillation in combination with other organic and functional cardiovascular disturb-

ances at the first examination of a thyrotoxic patient does not offer grounds for assuming that it has been caused by thyrotoxicosis and not by an earlier lesion of the mitral valve. To establish the original cause of auricular fibrillation in such cases it is important to make a roentgenoscopic measurement of the size of the left atrium and the right heart, which in mitral stenosis are considerably enlarged, while in thyrotoxicosis the main alterations take place in the left ventricle. It should be added that a differential diagnosis here is important only in the sense of the proper appraisal of the patient's condition and not as regards the urgency of antithyrotoxic measures, since thyrotoxicosis which developed against the background of a sick heart accelerates the insufficiency of the latter and under all circumstances demands urgent active treatment.

Naturally, auricular fibrillation and other cardiovascular alterations, observed for the first time in a patient with an enlarged thyroid, in the absence of other precise thyrotoxic phenomena and indications of thyrotoxicosis in the anamnesis, cannot be confidently credited to the thyroid without a special study of its functional condition. This point must be stressed because experience shows that in cases when only the thyroid gland is enlarged some or other disturbances in the organism, including cardiovascular alterations, are often credited to the thyroid gland without sufficient reason.

Caution is also required in evaluating the oedema of legs and other parts of the body observed in severe thyrotoxicosis. Of course, this might be a manifestation of cardiac insufficiency, but not infrequently a big part in its genesis is also played by increased vessel permeability which occurs in thyrotoxicosis. That is why in thyrotoxicosis oedema may not necessarily be an indication of the insufficiency of circulation.

Lesion of the myocardium in thyrotoxicosis is designated by the term "thyrotoxic heart". Electrocardiographic changes in thyrotoxicosis are characterised by high waves

T and P; if the disease is prolonged wave T flattens, while wave P remains high and only after effective cure are both waves normalised. In severe cases the electrocardiogram shows the degree of disturbance of atrioventricular conductivity and the nature of the derangement of the rhythm in various kinds of thyrotoxic arrhythmias.

Exophthalmos (Fig. 4) for a long time has been regarded as an indispensable symptom of pronounced forms of thyrotoxicosis both because it is part of the Basedow triad and because it is frequently the first symptom which attracts the patient's attention and brings him to the doctor. But data of many Soviet and foreign authors and particularly the observations conducted at the All-Union Institute of Experimental Endocrinology have shown that in severe thyrotoxicosis exophthalmos and other eye symptoms which will be discussed later may be absent (according to data of the All-Union Institute of Experimental Endocrinology, these symptoms are absent in 21 per cent of the patients). Moreover, exophthalmos even in case of an enlarged thyroid with symptoms of thyrotoxicosis is not always due to the latter. Prominence of the eyes might be of familial or myopic origin; it might

Fig. 4. Patient, age 51, with severe thyrotoxicosis. Exophthalmos, Graefe's sign.

be a direct result of a cerebral lesion of respective localisation which caused thyrotoxicosis. It is important to bear all this in mind both in appraising the symptoms of thyrotoxicosis in the dynamics of their development and reaction to treatment and in the choice of special methods of medication. All the more critical must the doctor be in exophthalmos of patients who, besides an enlarged thyroid gland, show no other thyrotoxic symptoms and there were none in the past (if there is thyrotoxicosis in the anamnesis exophthalmos might be residual), or when the thyroid is not palpable. This point must be stressed because to this day doctors often regard exophthalmos as an indispensable symptom of thyrotoxicosis and overlook the latter when there is no abnormal prominence of the eyes; or, on the contrary, on the basis of exophthalmos alone they groundlessly orient themselves solely on thyrotoxicosis in their diagnosis and treatment, forgetting other conditions of which abnormal protrusion of the eyeball might be a symptom.

D. I. Fridberg asserts that in thyrotoxic exophthalmos, in contrast to encephalitic exophthalmos, there are never any luxation of the eyeball or lens, keratitis, pain and burning of the eyes, conjunctival injection and chemosis, lacrimation and corneal ulcers. But many Soviet and foreign authors describe such phenomena in thyrotoxic exophthalmos as well (M. R. Weber, V. G. Baranov, A. T. Kameron and others) (Fig. 5). Therefore this question requires additional study, but at the same time we can agree with Fridberg's fully substantiated

Fig. 5. Patient, age 28, with severe thyrotoxicosis. Acute exophthalmos and keratitis.

assertion that the paresis of the upward view is characteristic of encephalitic and not of thyrotoxic exophthalmos (Fig. 6,7). Special caution should be exercised in judging the thyrotoxic genesis of unilateral exophthalmos which

Fig. 6. Patient, age 32. Slight thyroid enlargement without derangement of its function. Encephalitis. Paralysis of upward view, wide opening of the palpebral fissures.

Fig. 7. Patient, age 30. Enlargement of the thyroid without derangement of its function. Encephalitis. Unilateral exophthalmos, paresis of upward view. Hyperemia and chemosis of the right eye.

may take place in thyrotoxicosis, but is observed much more rarely than two-sided and is more often a result of unilateral intraocular alterations of a compressional or inflammatory nature (tumour, abscess, venous congestion). According to data of Sattler and N. A. Shereshevsky, unilateral exophthalmos is observed in 10 per cent of patients with thyrotoxicosis.

Many investigators have taken an interest in the genesis of exophthalmos in thyrotoxicosis, but there is no full clarity on this question as yet. Formerly many authors headed by Basedow expressed the opinion (to which lately

V. G. Baranov subscribed) that exophthalmos in thyrotoxicosis is caused by the protrusion of the eyeball from the orbit by the proliferating retrobulbar fat cellular tissue. This is contradicted by the rapid development of exophthalmos in a few hours or days observed at times. Other supporters of the protrusion theory explain it by retrobulbar venous congestion (V. A. Oppel, Graefe, Sattler) or by arterial hyperemia (M. G. Matusov, Möbius). An argument presented against this view is the absence, as a rule, in exophthalmos of pulsation of the eyeballs and changes of the cellular tissue inherent in the above vascular alterations.

On the basis of experiments conducted by Claude Bernard who induced exophthalmos by irritating the cervical sympathetic nerve, V. D. Shervinsky, Kraus and lately N. A. Shereshevsky consider that in thyrotoxicosis the bulging of the eyeball arises as a result of contraction of the orbital muscle. But they do not take into consideration the fact that in man this muscle is very weakly developed and that in thyrotoxicosis other symptoms observed in experiments of Claude Bernard in irritating the cervical sympathetic nerve, specifically the dilatation of the pupil, are absent.

S. A. Spector was the first to voice the view about the cerebral muscular genesis of thyrotoxic exophthalmos. He thinks that the mechanism of exophthalmos in thyrotoxicosis consists in the supertonicity of the oblique muscles owing to the lesion of the extensor sympathetic centre in the tuber cinereum. The oblique muscles draw the eyeball from the orbit and are its extensors. Spector was the first to notice in thyrotoxicosis the symptom of pain at the points where the oblique muscles are attached to the sclera. Fridberg observed in thyrotoxic unilateral exophthalmos an increase of tendon reflexes and the appearance of pathological reflexes on the side opposite to the more protruding eyeball. This gave him grounds for speaking about the localisation of the focus causing the

alternating syndrome within the bounds of medulla oblongata (at the level of the anterior part of the corpora restiformia), with the exophthalmos on the side of the focus and phenomena of pyramidal insufficiency on the opposite side. On the basis of neurological and autopsy data, Fridberg also considers it possible for moderate exophthalmos to arise in lesion of the nucleus of the oculomotor nerve. Fridberg's views about the ways in which the cerebral impulses determining exophthalmos are realised in the eye itself are less explicit and convincing.

Thus the clinical picture of exophthalmos has been well studied in respect of its differential diagnosis, but on the question of its genesis there is no single opinion as yet.

In addition to exophthalmos a number of other eye symptoms are observed in thyrotoxicosis. The Möbius' sign consists in a derangement of convergence, i.e., the inability to fix the eyes on objects at a near distance owing to the prevalence of the tonus of the oblique muscles over the tonus of the converging muscles recti oculi mediales (the tonus of the muscles recti oculi laterales in convergence is always weakened). This sign cannot be determined, as some authors assume, by the weakness of the muscles recti oculi laterales since in thyrotoxicosis no diplopia is usually observed. Graefe's sign (see Fig. 4) is manifested in the tardy movement of the upper lid in looking downward, as a result of which a white strip of the sclera becomes visible between the upper lid and the iris. This symptom is explained by the supertonicity of the muscle which raises the upper lid. It differs from exophthalmos for its genesis and in the clinic is not always encountered simultaneously with exophthalmos. Thus, Graefe's sign might be absent in expressed exophthalmos and at the same time be observed in the complete absence of exophthalmos. Stellwag's sign consists in infrequent blinking and it appears when it is hard for the orbicular muscle to overcome the elevated tonus of the muscle which lifts the upper lid.

Fridberg explains the Möbius' and Graefe's signs as a disturbance of synkinesia, that is, the combined movement of both eyes in case of Möbius' sign and of the upper lid and the eyeball in case of Graefe's sign. Disturbance of synkinesia might arise in the lesion of the nuclei of the facial and oculomotoric nerves and the disturbance of the connection between these nerves effected through the posterior longitudinal bundle. Fridberg regards Stellwag's sign as a partial manifestation of amimia owing to lesion of subcortical structures.

Nor is there one opinion about the mechanism in thyrotoxicosis of Dalrymple's sign noticed long ago. It is expressed in the wide opening of the palpebral fissure, which imparts to the patient's face an expression of fright, wrath or concentration (Fig. 8). A strip of the sclera remains uncovered in the upper part of the eyeball, like in Graefe's sign, and at times also in the lower part. A combination of this sign with exophthalmos is not obligatory. Spector, like a number of other authors, explains this sign by the elevated tonus of the smooth muscle of the lids innervated by the sympathetic nerve. Fridberg supposes that of the two groups of muscles which determine the position of the lids and consequently the normal size of the palpebral fissure, the enlargement of the palpebral fissure is caused not by the spastic contraction of the tar-

Fig. 8. Patient with severe thyrotoxicosis. Exophthalmos, wide palpebral fissures. Concentrated wrathful look.

sal muscles of the lids, but by paresis of the orbicular muscle which is innervated by the facial nerve. This is also demonstrated by the fact that the enlargement of the palpebral fissure in thyrotoxicosis does not yield to treatment by pachycarpine.

In pronounced thyrotoxicosis, just as in any severe disease, a number of organs are drawn into the pathological process. We shall discuss only those organs which are affected most frequently and not only in severe but also moderately severe thyrotoxicosis. These include in the first place the gastro-intestinal system. According to data of various authors (Sattler, Curshmann), it is affected in 30 to 60 per cent of the patients with thyrotoxicosis and, according to data of the All-Union Institute of Experimental Endocrinology, in 37 per cent of the patients. Particularly painful for patients are the so-called Basedowic *krises*, i.e., attacks of acute pain in the stomach, liver and various parts of the intestines or all over the abdomen. Such attacks, although they relatively seldom occur (according to data of the All-Union Institute of Experimental Endocrinology, among 20 per cent of the patients) for their intensity and localisation may furnish grounds for wrong diagnosis (liver and renal colics, ulcer of the stomach, acute appendicitis) and at times to unjustified surgical intervention. Together with attacks of pain, there is also vomiting, which makes the attacks especially painful. Vomiting may be observed in thyrotoxicosis independently of attacks: according to data of the All-Union Institute of Experimental Endocrinology, among 4 per cent of the patients and according to data of some authors (Sattler and others), up to 15 per cent.

Diarrhea, transitory or steady, slightly or strongly pronounced, is more frequent. According to data of the All-Union Institute of Experimental Endocrinology, it is found in 31 per cent of the patients. Among a small number of thyrotoxic patients there is steatorrhea (fat indigestion), which should be credited to the simultaneous disturbance

of the excretory function of the pancreas with a decreased hydrolysis and absorption of fat and, possibly, to the more rapid movement of the food masses in the intestinal tract. Constipation is less frequent than diarrhea. In such cases the abdomen is drawn in, the transverse and sigmoid intestines and sometimes the caecum are palpable as spastically contracted, the number of bowel movements is decreased and there is a pipe-stem stool. The acidity of gastric juice in most cases is elevated, especially at the beginning of the disease, but it is also lowered at times; complete achylia gastrica is also observed. The appetite of the patients is unstable: the patients are either hungry, "like wolves", or (in severe forms of thyrotoxicosis) have no appetite at all and the patients have to be fed by force.

These gastro-intestinal disarrangements in thyrotoxicosis are determined by the excessive positive impulses of the higher parts of the central nervous system, which brings about greater motor and secretory function of the gastro-intestinal tract. Hyperkinesis is manifested in diarrhea and when strongly pronounced, in spastic constipation and attacks of pain owing to periodic spasms in the pyloric part of the stomach and cramps in the intestine. Gastro-intestinal disorders in thyrotoxicosis, even if they are of considerable intensity and duration, are most frequently of a functional, reversible nature; under the influence of treatment they pass, together with other thyrotoxic phenomena, which confirms their neurogenic genesis.

In thyrotoxicosis the liver is frequently drawn into the pathological process. Special attention to this point has been paid ever since the study of the diverse activities of the liver with the aid of various diagnostic tests has become widespread in medical practice.

The function of the liver was found to be disturbed in a number of patients with thyrotoxicosis even when usual physical methods of examination did not indicate any liver

pathology. This problem was the subject of a dissertation for the degree of candidate of science by M. A. Alekperov (All-Union Institute of Experimental Endocrinology). Results of similar observations have been published by S. F. Mandl. Both these authors, like others, agree that the extent of functional insufficiency of the liver both for number of disturbed functions and for their degree depend on the severity and duration of thyrotoxicosis. In such cases the antitoxic, glycogenosynthetic, glycogenopexic, albumino, cholesterolo, prothrombino-genetic and pigmentoregulatory functions of the liver are affected.

Derangement of the role of the liver in protein metabolism, according to data of the two authors, in thyrotoxicosis is expressed mainly not in a change in the general quantity of serum protein, but a lowered albumin-globulin ratio owing to a reduction in the number of albumins, in the formation of which the liver takes an active part, and relative increase in globulins, especially, gamma globulin. The prothrombinogenetic insufficiency of the liver is manifested, according to Alekperov, not only in the low initial level of prothrombin, but also in the imperfect prothrombin reaction to vicasol loading. Disturbance of the pigmentary exchange is manifested more often in urobilinuria than in hyperbilirubinemia.

Hyperbilirubinemia is not the only alteration observed in thyrotoxicosis. In case of a severe course of this disease jaundice of various origin might appear—cellular-hepatic (parenchymatous hepatitis), cardiac (on the basis of congestion in the liver during cardiac insufficiency) and hemolytic. The last is especially unfavourable prognostically. Subacute yellow atrophy of the liver and death from a hepatic coma have also been described in cases of thyrotoxicosis.

Autopsy findings in thyrotoxicosis have disclosed in the liver atrophic, degenerative and necrotic changes, fat infiltration, phenomena of parenchymatous and interstitial

hepatitis, hypertrophic, and more seldom atrophic, cirrhosis.

There is no single view on the causes of hepatic lesion in thyrotoxicosis. An opinion has been expressed concerning the direct toxic influence of the excessively produced thyroxin on the parenchyma of the liver. Other ways of thyroxin action on the liver have also been indicated. It is known that thyroxin, like adrenalin, raises glycogenolysis in the liver and leads to a depletion of its glycogen stores. Hence the functional insufficiency of the liver and the lowered resistance to injurious influences. Thyroxin, activating oxidation processes in the organism, leads to hepatic hypoxia with all its consequences for the functional state of the liver. It should be assumed that the diverse pathological changes in the liver, observed in thyrotoxicosis, hardly speak of their single genesis. It is more probable that not each of the indicated factors separately, but all of them in their totality, determine liver lesions in thyrotoxicosis. It should be added that the functional alterations of the liver in thyrotoxicosis, even when considerably pronounced, are in most cases regressive when the main disease is actively treated.

The kidneys are usually not involved in thyrotoxicosis. Polyuria observed at times is connected with changes in water metabolism in this disease.

Many observers have studied the influence of thyrotoxicosis on the morphological constituents of the blood. All of them have arrived at the conclusion (this conforms with our observations as well) that in thyrotoxicosis the blood can be absolutely normal, but frequently, especially in pronounced forms of thyrotoxicosis, in the white blood there is leukopenia, neutropenia, relative lymphocytosis and more rarely absolute lymphocytosis and also monocytosis and, still more rarely, eosinophilia. The number of thrombocytes, especially in severe thyrotoxicosis, is lowered. In the red blood there is a small decrease in

the number of erythrocytes and haemoglobin and in some cases, even an increase. H. Zondek has succeeded in inducing in healthy people an increase in the number of erythrocytes in peripheral blood by the administration of thyroidin. Haemolytic anaemia is rare and it is found only in very severe forms of thyrotoxicosis. According to data of the All-Union Institute of Experimental Endocrinology, in most patients with thyrotoxicosis the E.S.R. is increased, especially in severe forms of the disease. Blood coagulation in thyrotoxicosis is most frequently retarded and its viscosity is decreased. Of all the changes in the blood in thyrotoxicosis lymphocytosis is the most frequent. Its origin is appraised differently: either as a consequence of irritation of the lymphatic apparatus by the excessively produced thyroxin or as a result of the transfer of the lymphocytes from the thyroid into the peripheral blood. We think it is more correct to regard lymphocytosis as one of the indications of the involvement of the adrenal cortex in the thyrotoxic syndrome and its insufficiency as a result of initial hyperfunction (see p. 66). Under the influence of active treatment the normal picture of the blood is restored. Lymphocytosis responds well to treatment with cortin.

Marrow blood formation in thyrotoxicosis has been studied thoroughly by D. Y. Shurygin and G. A. Zviadadze. According to data of these authors, hyperplasia of the leucopoietic tissue has been observed in bone marrow, with the leucoblast-erythroblast ratio being higher than normal. Moreover, retardation of the maturing of granulocytes in the promyelocyte, myelocyte and metamyelocyte stages has been observed, and a lag in the maturing of the protoplasm of the granulocytes as compared with the formation of the nucleus has been established. These changes in the leucopoietic function of bone marrow correspond to neutropenia and leukopenia in the peripheral blood. Disturbances in the maturing of neutrophilic granulocytes in bone marrow, according to data of Shurygin,

are noticed much earlier than the corresponding changes in the peripheral blood.

An increase in the eosinophilic elements of the bone marrow proceeds at the expense of myelocytes and metamyelocytes. Eosinophilia of the peripheral blood may also correspond to these changes. The number of lymphocytes in a bone marrow punctate rises and reaches up to 30 per cent (instead of 4 to 9 per cent); in the peripheral blood, however, lymphocytosis, more often relative, is found only among some of the patients. Megakaryocytes in bone marrow are either totally absent or found in negligible quantities in all thyrotoxic patients, according to data of Zviadadze. According to data of Shurygin, their number rises considerably in cases of severe thyrotoxicosis, while thrombopenia of the peripheral blood is caused by a disturbance of their normal maturation. The content of erythroblasts in bone marrow is normal or declines. Moderate erythropenia is observed in the peripheral blood when there is considerable retardation in their maturing.

The dependence of disturbances in marrow blood formation and changes in the morphological composition of the blood in thyrotoxicosis is confirmed by the fact that when thyrotoxicosis is successfully cured surgically (Zviadadze) or by methylthiouracil (Shurygin) the disappearance of thyrotoxic phenomena is accompanied by the restoration of the normal picture of marrow blood formation and the cellular constituents of the peripheral blood.

Muscle fatigue (complaints of patients about buckling of the legs when walking, difficulty in lifting the extremities, etc.) is often observed (according to our data, in 55 per cent of the patients). Some authors regard myopathy as one of the initial symptoms of this disease. Zondek has put forward the peripheral theory of the pathogenesis of thyrotoxicosis. He assumes, as pointed earlier, that the thyrotoxic process may be determined by the primary loss by muscle tissue of the ability to utilise oxygen and the resultant secondary hyperplasia and thy-

roid hyperfunction with the surplus secretion of thyroxin, which intensifies the tissue oxidation processes. Such a conception is theoretically inacceptable since it places the gaseous exchange outside the regulating influence of the central nervous system and its higher parts. Moreover, it has not been justified practically by our clinical observations, according to which muscle fatigue as an initial symptom of thyrotoxicosis is found only in 8 per cent of the patients.

A special study of the neuromuscular apparatus in thyrotoxic patients made at the All-Union Institute of Experimental Endocrinology (Fridberg) has shown that in moderately severe thyrotoxicosis the proximal parts of the extremities (the scapulo-brachial and lumbo-femoral girdle) are affected, the tonus and electrosensibility of the muscles are lowered, while a corresponding derangement of sensitivity is absent; atrophy of the muscles is seen primarily in the scapulo-brachial girdle, and in severe forms of the disease paresis of the muscles assumes a generalised character. Degeneration of the effectory cells of the anterior horns of the spinal cord has been found in autopsy material and also in experimental thyrotoxicosis. All this furnishes grounds for considering that in thyrotoxicosis muscle disorders are due to a lesion of the spinal cord.

The above data include muscle disorders in thyrotoxicosis in one group with other thyrotoxic symptoms, whose general pathogenic feature is lesion of the motor nerve elements of the cerebrum and spinal cord in connection with the derangement of the normal corticovisceral regulation. Besides severe degenerative processes, changes in the respective parts of the cerebrum and spinal cord might be only of a functional nature This explains the reversibility, under the influence of treatment, of the clinical symptoms caused by them.

Iodine metabolism in thyrotoxicosis is of the greatest interest in view of the role iodine plays in the synthesis

of thyroxin. Iodine enters the body with food and drinking water. Green vegetables, milk, eggs, sea and freshwater fish are the foods which are richest in iodine. From the intestinal tract iodine passes into the blood and from there into the tissues of the organism. Iodine is contained in all organs, but most of all in the endocrinal glands, chiefly in the thyroid which accounts for 1/5-1/10 of the iodine in the organism; man has on the average 0.0025 g of iodine per g of raw thyroid gland. Of this quantity, the active element of the thyroid, thyroxin, contains from 36 to 73 per cent of the iodine. The content of iodine in the blood during the normal function of the thyroid ranges from 8 to 14 gamma per cent (in round figures), but it can reach up to 20 gamma per cent; in winter it drops to 6.3 gamma per cent on the average. Of the iodine in the blood 65 per cent (from 3.5 to 8 gamma per cent) is organic and about 35 per cent is inorganic. In addition to the seasons of the year, the content of iodine in the organism is influenced by sex, age, periods of the menstrual cycle, pregnancy, child-birth, breast-feeding, etc., in other words, all conditions which physiologically affect the function of the thyroid. Particularly noticeable changes in the content of iodine in the thyroid and the blood are seen in the hyperfunctioning or hypofunctioning thyroid. In thyrotoxicosis the quantity of iodine both in the thyroid and in the blood rises (especially of organic iodine) and reaches from 30 to 50 gamma per cent and higher. It is interesting that in thyroid hyperfunction the content of iodine rises in the hypophysis and the subthalamic region of the cerebrum which also participate in the regulation of iodine metabolism. Iodine is excreted from the organism (in a somewhat smaller quantity than enters it) chiefly through the kidneys and the skin, and also through the intestine and the respiratory tract. In thyrotoxicosis the excretion of iodine increases. In hypothyroidism both the content of iodine in the thyroid

and blood, just as its excretion from the organism, decrease.

The accumulation of iodine in the organism, primarily in the thyroid gland, the change in the content of iodine in the gland and in the blood, depending on the functional state of the thyroid, indisputably point to the role of the thyroid in the cerebro-endocrinal regulation of iodine metabolism. This is also confirmed by the fact that after the excision of the thyroid gland the dependence of the content of iodine in the blood and urine on outside influences is more pronounced than under normal conditions.

In pronounced forms of thyrotoxicosis disturbance of carbohydrate metabolism in the form of hyperglycemia and glycosuria is observed. But in mild thyrotoxicosis, too, easily induced alimentary and adrenal hyperglycemia and glycosuria have been seen by some authors (Kraus, Ludwig, and Chvostek). Wahlberg attaches great diagnostic importance to alimentary hyperglycemia as the earliest symptom of thyrotoxicosis, which is frequently manifested before the appearance of other thyrotoxic symptoms, including changes of the basal metabolism. In thyrotoxicosis the glucose tolerance curve after the load shows an elevation higher and longer than the norm. The higher content of sugar in the blood and urine in thyrotoxicosis is explained by the sympathicotropic action of thyroxin which, like adrenalin, promotes glycogenolytic processes in the liver and the removal of sugar from it. Experimentally, a depletion of the glycogen stores in the liver under the action of thyroidin was seen together with hyperglycemia. A decrease in the content of glycogen in the muscles, including the myocardium, was also observed as a consequence of disturbing the process of resynthesis of glycogen from lactic acid, the content of which in the blood rises in this connection.

It cannot be denied that the insular apparatus of the pancreas too takes part in the hyperglycemic reaction in

thyrotoxicosis. Holst noted a decrease in the weight of the pancreas and fibrous changes in its insular apparatus in 6 out of 10 patients with Basedow's disease. After thyroidectomy in Basedow's disease Falta, on the contrary, observed hypertrophy and hyperplasia of the islets of Lagerhans. The extent to which this symptom is pronounced evidently depends on the degree to which the pancreas participates in the thyrotoxic disturbance of carbohydrate metabolism. Alongside hyperglycemia and glycosuria which can be only alimentary, real pancreatic diabetes mellitus might develop in thyrotoxicosis. While thyrotoxic hyperglycemia and glycosuria pass under the influence of anti-thyroid treatment, together with other thyrotoxic symptoms, pancreatic diabetes mellitus which arises following thyrotoxicosis, or before it as might also be the case, demands special treatment. The doctor must not limit himself to antithyroid medication; nevertheless in such cases amelioration of the thyrotoxic phenomena under the influence of medicamentous or surgical treatment favourably affects the course of diabetes mellitus. That is why the latter cannot be a contraindication to subtotal thyroidectomy if the thyrotoxic patient requires it.

The lipid metabolism of patients with thyrotoxicosis changes towards an elevation of neutral fat in the blood and its decrease in the liver and lipid depots. This is explained by the greater transfer of lipid from the periphery to the glycogen-depleted liver and the more intensive burning up of fat in it. This leads to a hyperketonaemic reaction, sharper than usual, to the introduction of fat (butter) and protein (curd) rich in lipotropic factors. The lesion of the liver itself, with the disturbance of its lipid regulatory function, probably facilitates hyperketonaemia in thyrotoxicosis.

Disturbance of the cholesterol metabolism in thyrotoxicosis is manifested in the depletion of cholesterol in the adrenal cortex and liver. There is greater excretion

of cholesterol in bile in unchanged form or in the form of cholalic acid, as a result of which in case of thyrotoxicosis there is an enrichment of the bile with cholesterol and bile acids, while in case of hypothyroidism there is a depletion of these substances.

The state of the protein metabolism is of especial importance in thyrotoxicosis. While loss of fat and dehydration of the organism lead only to a loss of weight, the general weakness and swift fatigue of which patients complain are determined by alterations of the protein metabolism, i.e., processes of increased catabolism and deamination of proteins. The nitrogen balance becomes negative. Its degree conforms to the severity of the disease. In very severe thyrotoxicosis it even leads to a marantic state of the patients. In thyrotoxicosis alterations of the protein metabolism are clinically manifested in elevated residual nitrogen of the blood which reaches up to 100 mg per cent (Weber), and also increased secretion of kreatine, kreatinine, ammonia and urea.

The viewpoint that alteration of the protein metabolism in thyrotoxicosis is secondary and is connected with greater catabolism of carbohydrates and lipids in the body cannot be considered as sufficiently substantiated. First, a conformance between the degree of alteration in these forms of metabolism is not always seen; second, the increased consumption of carbohydrates and fats in thyrotoxicosis can only elevate somewhat the nitrogen balance, but cannot fully normalise it. The opinion (of Chvostek and others) that the thyroid hormone directly influences intracellular protein metabolism by activating the proteolytic cellular enzymes, is more grounded. This is confirmed by studies *in vitro* and *in vivo* (N. M. Rudenko, Veil and Landsberg). S. M. Leites and L. L. Klaf, taking into account the active reaction of the medium in which thyrotoxic proteolysis is especially pronounced, assume that it is a case of greater activity of the tryptase enzyme in thyrotoxicosis.

Water metabolism in thyrotoxicosis is deranged. The organism is dehydrated. Patients eliminate up to ten litres of urine daily. The elimination of water, according to the Volhard and Fahr test, is much higher than usual: after three hours all the ingested water is eliminated, and not 60 per cent as is normally the case. Patients with thyrotoxicosis abundantly eliminate water not only through the kidneys but also through the skin which is moist all the time and has a reduced electric resistance, as well as through the lungs. Alteration of the water exchange in thyrotoxicosis is mainly connected with reduced hydrophilia of the tissues and cells owing to an alteration of the other forms of metabolism in them. In this category, too, are greater proteolysis and change in the oncotic blood pressure, increased release of sodium chloride by the tissues and its excretion in urine, the loss of glycogen and cholesterol by the organism. The tissue origin of dehydration of the organism in thyrotoxicosis is confirmed by the hydremia which occurs simultaneously with greater diuresis. As for the vessel dilatation observed experimentally in hyperthyroidism, it shows that here the kidneys, too, influence diuresis.

The particular intensity of metabolic processes in patients with thyrotoxicosis leads to greater consumption of oxygen by their tissues even in a state of rest, i.e., to an elevation of their basal metabolism. And this is the case not only because in thyrotoxicosis the organs, even in a state of rest, work more actively, but also because in the cell itself metabolism is intensified. Opinions differ on the mechanism of action of thyroxin on cellular metabolism. Some authors assume that thyroxin affects directly the processes of cellular metabolism, while others hold that the action of thyroxin is secondary. According to Eppinger, for example, thyroxin raises capillary permeability, causing thereby tissue oedema and thus hindering the access of oxygen into the cell; oxygen starvation of the cells, in its turn, leads to irritation of the respira-

tory centre and to greater utilisation of oxygen by the organism.

Before measuring the basal metabolism of the patient, the latter is kept on a protein-free diet for two days. The measurement is made in the morning in a fasting state, with the patient in a lying position and a complete state of rest. Special apparatuses of Krogh, Knipping or Holden are used for measuring the quantity of oxygen utilised by the patient in a unit of time (Krogh apparatus) or also the excreted carbon dioxide—the respiratory quotient (the Knipping or Holden apparatus). Then by the calory equivalent of oxygen the number of heat calories used by the patient is established. A comparison of the obtained data with a special table of similar data for a healthy person of the same sex, age, weight and height, expressed in percentages, characterises the value of the basal metabolism of the patient. In thyrotoxicosis it usually exceeds the norm (norm of from —10 per cent to +10 per cent). In very severe thyrotoxicosis the value of the basal metabolism might reach up to +100 per cent and more, but full conformity between high basal metabolism and the severity of thyrotoxicosis is not frequent. Any alteration of cardiovascular activity, respiration, the composition of the red blood, etc., affecting the utilisation of oxygen by the tissues, is reflected in the valuc of the basal metabolism. That is why in judging the severity of thyrotoxicosis, the doctor must not guide himself solely by the basal metabolism, especially if its values do not coincide with the clinical picture. Nevertheless, the level of the basal metabolism can serve as an objective criterion in evaluating the dynamics of thyrotoxicosis in connection with the treatment applied and also partly in differential diagnosis between thyrotoxicosis and neurosis of a general type in patients with a thyroid gland that had become enlarged earlier. It should be borne in mind that a nervous disorder might also increase the basal meta-

bolism, but not to the same extent and not so stably as thyrotoxicosis.

According to data of Y. Y. Reznitskaya, the specific dynamic action of all kinds of food is elevated considerably in thyrotoxicosis, in the first place of proteins, then carbohydrates and fats.

The elevation of all kinds of metabolism in thyrotoxicosis, especially of lipid and water exchange, with the more intense burning up of fat and loss of large quantities of water, naturally leads to a loss of weight and flesh. In severe forms of the disease the weight of the patient may drop by as much as 50 per cent and more as compared with the normal weight corresponding to his height (Fig. 9). Considerable and quick loss of weight is frequently the first symptom of thyrotoxicosis that draws the attention of the patient. In severe thyrotoxicosis it can develop at times much sooner than the other symptoms. With the simultaneous elevation in protein catabolism, the emaciation and weakness of patients are such that it is hard for them to move about, on the basis of this symptom some authors single out a special marantic form of thyrotoxicosis.

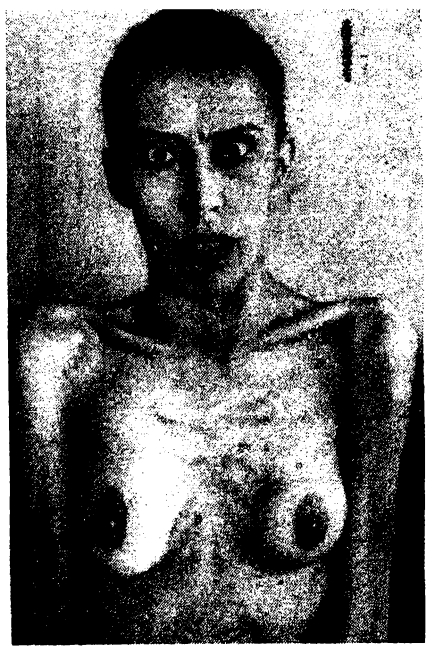


Fig 9 Patient, age 29, with severe thyrotoxicosis Acute emaciation, loss of weight (in relation to height), 58 per cent.

In very rare cases thyrotoxicosis is accompanied by a gain of weight. This is so-called "fat Basedow" (Fett-Basedow). This, of course, does not apply to patients who had suffered from obesity prior to the onset of thyrotoxicosis, while the latter did not as yet bring about a loss of weight. This refers to patients of normal weight, in whose case parallel with the growth of thyrotoxic phenomena a gain in weight is noticed. This paradoxical phenomenon is explained in different ways. Some authors (Zondek) regard "fat Basedow" as dysthyroidism and obesity of such patients, as the only hypothyroidal component of dysthyroidism.

Pineles regards obesity in thyrotoxicosis as hypercompensation, i.e., an extremely pronounced defensive reaction of the organism against the loss of weight threatening it under the influence of excessively produced thyroxin. Pineles has not disclosed the way this hypercompensation operates. We consider it possible to voice the assumption that in "fat Basedow" we have such a state of the cerebral mechanism regulating the lipid metabolism in which thyroxin as the excessively positive irritant may cause a responsive inhibitive reaction (transmarginal inhibition). This form of thyrotoxicosis must be borne in mind so that a gain in weight in thyrotoxicosis should not make the doctor doubt the existence of thyrotoxicosis and cause him to direct the treatment along the wrong path. In such cases antithyroid medication is applied and if it is effective obesity disappears together with other thyrotoxic symptoms.

In addition to metabolic alterations a number of cerebral disorders are also seen in thyrotoxicosis. Among these are disturbances of thermoregulation with an increase of temperature, insomnia, tremor of the fingers of the extended hands and of the entire body, neuropsychic disorders.

A rise of temperature is not an obligatory symptom in thyrotoxicosis—it may be absent or be insignificant in

the severe form of thyrotoxicosis or reach 37.6 to 37.8° C in the mildly pronounced form of the disease. The nature of the fever is thermoneurotic; it is a reaction of the labile thermoregulating centre to thyrotoxicosis. The pyramidon test does not act on the temperature, but the temperature is reduced, together with other thyrotoxic symptoms, under the influence of anti-thyroid medication. Disturbance of thermoregulation in patients with thyrotoxicosis is also expressed in that they are hypersensitive to heat and thermotherapy, under the influence of which the thyrotoxicosis may be exacerbated. In this category too is hyperhidrosis which may be so pronounced as to give the patients no rest day and night.

Insomnia is one of the most painful symptoms of thyrotoxicosis. According to our data, it is seen in 45 per cent of the patients. Sleep is restless, with bad dreams, and it does not give a rest to the cortical cells, whose working capacity is not fully restored, which worsens the course of the pathological process.

Tremor of the entire body and of its separate parts (extremities, head, body, lids) is frequent in thyrotoxicosis and, according to our data, is seen in 87 per cent of the patients. Especially characteristic is the fine involuntary tremor of the fingers of the extended hands (with the relaxed wrist), which increases in case of emotional strain, fatigue and exacerbation of the process. These specific features of thyrotoxic tremor should be known because they to some extent help to differentiate it from tremor in case of a number of nervous ailments.

A psychic change is almost always observed in pronounced thyrotoxicosis. Patients are very excitable, irritable, fussy, restless and a frequent change of mood is observed—from groundless gayety to similarly groundless melancholy. According to our data and data of other authors, true psychoses (maniacal state, hallucinations, etc.) are seen very seldom in thyrotoxicosis.

A. G. Vasilyeva, utilising the motor speech methodics

of A. G. Ivanov-Smolensky, noticed in thyrotoxic patients at the clinic of the All-Union Institute of Experimental Endocrinology a weakening of the reactivity of the cortical cells and reduction of the limit of their working capacity, disturbance of the mobility of nervous processes, a certain weakening of the processes of active inhibition and the existence of transmarginal inhibition. Nervous activity improves after thyroidectomy, but full normalisation of cortical processes is slow. According to data of V. G. Baranov (method of blinking conditioned reflexes, after I. I. Korotkin), in thyrotoxicosis both processes of excitation and inhibition are affected, but the latter especially deeply.

All the numerous symptoms discussed above are not always in evidence in their aggregate in thyrotoxicosis. When the thyroid is enlarged in one or another degree, frequently only two or three symptoms are noticeable and, moreover, not the most vivid; tachycardia, however, is seldom absent. Such forms of thyrotoxicosis with an incomplete symptom complex are called forme fruste. At times they present considerable difficulties for differential diagnosis, especially if the thyroid is not greatly enlarged. The doctor must know such forme fruste so as to avoid error in diagnosis.

The severity of thyrotoxicosis is determined not by the number of symptoms comprising the thyrotoxic syndrome, but by the degree of pronouncement of its separate clinical manifestations and, chiefly, by the general state of the patient and his working capacity. For degree of severity thyrotoxicosis is differentiated into mild, moderately severe and severe forms. If, for example, the patient's pulse has 90-100 beats per minute, the weight loss is 10-15 per cent, the nervous excitation is somewhat elevated, but the working capacity has not been reduced appreciably, it is a mild form of thyrotoxicosis. In moderately severe thyrotoxicosis the pulse reaches 120 beats per minute, the weight loss runs up to 20 per cent, ner-

vous excitation is elevated considerably and working capacity is partly reduced. In severe thyrotoxicosis the pulse has 120-140 beats per minute, auricular fibrillation is often seen, the weight loss reaches up to 50 per cent as compared with normal, there is oedema owing to greater permeability of the vascular walls, nervous excitation is highly elevated and there is total loss of working capacity. The approach is similar in assessing the other symptoms.

We cannot agree to the proposal of Baranov to designate mild, moderately severe and severe forms of thyrotoxicosis as thyrotoxicosis of the I, II and III degrees. Both in Soviet and foreign literature the term "degree" is applied for designating the size of the thyroid gland and to put new meaning into this term could only lead to confusion. Baranov's apprehensions that a diagnosis "severe form of thyrotoxicosis" would inevitably have a depressing effect on the patient are not warranted. Patients are usually frightened or reassured not by the name of their disease, but by the conception they gain about it in conversation with the doctor. Moreover, if the degree is to be used only for designating the severity of thyrotoxicosis, it will be necessary to find a new term for the size of the thyroid gland, which must not be ignored, especially in the dynamic aspect either for prognostic or therapeutic considerations.

The symptoms characterising thyrotoxicosis either arise suddenly and then the disease assumes a severe course, or they develop gradually and then the thyrotoxicosis is of a chronic nature, with remissions and relapses alternating over many years. In conformity with this, there are acute and chronic forms of thyrotoxicosis. A peculiar rapid exacerbation of thyrotoxic phenomena (thyroid storm) may suddenly set in against the background of chronic thyrotoxicosis. The clinical manifestations of such a storm are expressed in strong nervous excitation, with a considerable rise of temperature, insomnia, nausea and

vomiting, a general restless state alternating with complete prostration, apathy, indifference to the environment, then loss of consciousness (thyrotoxic coma) and death. The origin of such conditions is explained differently: they are associated with acute functional insufficiency of the liver (at times jaundice and cholemia are seen, and the autopsy reveals lesions of the liver), of the adrenals and thymus gland, with cerebral disturbances which develop under the influence of thyrotoxicosis. So far, however, there is no clarity on this question since a lesion of at least one of the enumerated organs is not always found during autopsy.

The division of thyrotoxicosis, according to the outward appearance of the patient, the prevalence of one or another symptom or age, as done by some authors, is utterly unjustified. Neither the appearance of the patients, nor the prevalence of some symptoms which, moreover, often change during the course of the disease, nor the age, are of decisive significance for evaluating the condition of the patient and offer no basis for any special therapeutic measure. As for age distinctions, according to observations conducted by D. D. Sokolov in the All-Union Institute of Experimental Endocrinology, no essential specific features of thyrotoxicosis among children have been noticed, except accelerated growth and processes of ossification, but the latter, of course, cannot occur among adults who stopped growing and in whose body the process of ossification has been completed.

The classification of thyrotoxicosis proposed by S. M. Milcu is fully acceptable. It is based on the principle of dividing thyrotoxicosis in the dynamic aspect by stages. Milcu differentiates four stages of thyrotoxicosis. The first stage (neurotic)—neurotic phenomena are in the foreground, while the thyroid is little enlarged; second stage (neuro-hormonal)—the thyroid is noticeably enlarged and thyrotoxic symptoms are distinctly pronounced; third stage (visceropathic)—the internal organs with their

organic lesions are drawn into the process; fourth stage (cachectic)—it is characterised by irreversible dystrophic alterations of systems and organs.

The name of the disease is likewise a question worthy of attention because there is no full unanimity of views on this score. At the beginning it was named Basedow's disease, after Basedow who for the first time clearly designated the triad included in its syndrome (goitre, exophthalmos, tachycardia). Subsequently it was established that the symptom complex of this disease goes far beyond the bounds of this triad and that this triad, except goitre, is not always obligatory even for the pronounced forms of the disease. Ever since Möbius has established the pathogenic connection of the disease with the hyperfunction of the thyroid, stressing the exceptional importance of the latter for the genesis and development of the entire symptom complex, the disease has been called hyperthyroidism. But even this name does not disclose the essence of the process in the present-day conception of it. We have already discussed the role of the central nervous system and its higher parts in the pathogenesis of thyrotoxicosis. The clinical picture of the disease is conceived as a cortico-vegeto-visceroneurotic syndrome, whose degree of pronouncement is not always adequate to the extent of thyroid hyperfunction; the reactivity of the nervous system, general and local, introduces essential adjustments in the symptomatology of the disease. Clinical observations demonstrated long ago that excision of a considerable part of the thyroid (subtotal thyroidectomy) does not always remove the symptoms of the disease and that the basal metabolism which to a certain extent reflects the function of the thyroid does not always conform to the severity of the disease, while the degree of pronouncement of thyrotoxic phenomena does not always coincide with the functional state of the thyroid established with the help of radioactive iodine. The term "thyrotoxicosis" (to be more exact, thyrotoxic neurosis) widely used at present,

reflects most fully the special importance—for the genesis and course of the disease—of the reactivity of the organism (of its nervous system) to the thyroxin excessively produced by the thyroid gland. But the term Basedow's disease continues to figure even now, particularly in foreign literature.

A number of methods has been proposed at different times for establishing the functional state of the thyroid gland in thyrotoxicosis. We shall not deal with those which are merely of historical interest and the diagnostic value of which is doubtful. We have already pointed to the significance of determining the basal metabolism. Let us examine one of the most reliable methods of diagnosing the function of the thyroid with the aid of radioactive iodine (I^{131}), which has been used in recent years. The method is based on the fact that tagged iodine introduced into the organism in any way, just as ordinary iodine, is absorbed from the blood mainly by the thyroid. The percentage of uptake increases in the hyperfunction of the gland and decreases in its hypofunction. This property of the thyroid has been definitely established and has been confirmed by numerous observations of Russian and foreign authors (M. A. Kopelovich and N. M. Draznin, M. N. Foteyeva, N. A. Gabelova, B. B. Rodnyansky, and D. M. Malinsky, Y. A. Kolli and N. A. Stegeman, Hamilton and others). The tracer dose of I^{131}, administered perorally by most Soviet authors, is 1-2 μC. The percentage of uptake by the thyroid gland of I^{131} introduced in the organism is checked after 2, 4 and 24 hours with the help of a Geiger-Müller counter. There are no big divergences among authors as to the average values of the I^{131} absorbed by the thyroid gland of healthy persons after the indicated periods of time.

According to the observations of Kolli and Stegeman (All-Union Institute of Experimental Endocrinology), in the normal thyroid gland the I^{131}, introduced in a quantity of 2 μC, is absorbed on the average after 2, 4 and 24

hours at the rate of 8.5, 12.3 and 21.3 per cent respectively. In thyrotoxicosis, owing to the increased production of thyroxin by the gland, the percentage of uptake of I^{131} is elevated considerably and may reach up to 80-90 per cent. Nevertheless, according to data in the literature and to our own observations, no conformity is observed between the severity of thyrotoxicosis and the degree of increase in the uptake of I^{131} by the thyroid. That is why some authors do not consider it possible to establish more precisely the severity of the thyrotoxicosis by the value of I^{131} uptake; others, however, on the basis of these indications, approximately single out mild forms of thyrotoxicosis and combine all other forms under the general term of "pronounced thyrotoxicosis". Thus Kolli and Stegeman give average values of tracer iodine uptake after 2, 4 and 24 hours respectively of 21, 26 and 37 per cent for mild forms of thyrotoxicosis and 39.6, 48.2 and 50 per cent respectively, for pronounced forms of thyrotoxicosis.

The average figures of I^{131} uptake in healthy persons and patients with light and pronounced thyrotoxicosis differ, but the range of individual fluctuation of the uptake values in patients of each of these groups is so great that if we were to judge the severity of the disease on their basis, clinically pronounced forms could be taken for mild ones or even for the normal functional state of the thyroid gland, while mild forms could be taken for pronounced thyrotoxicosis. That is why a number of authors (Kolli and Stegeman, Rodnyansky and Malinsky, Gabelova) advise doctors, in analysing data of the uptake of the tracer radioiodine dose, to guide themselves not by the absolute figures of absorption but by the uptake curve. A gradual elevation of the curve, from the beginning of I^{131} absorption to the end of the investigation, is characteristic of a normal functional state of the thyroid; a greater elevation of the curve, especially in the first hours after the administration of I^{131}, with a subsequent more gradual elevation, is characteristic of mild thyrotoxicosis; a very high

elevation of the curve in the first 2-4 hours and then either maintenance of the achieved level throughout the investigation or, more seldom, a certain decrease towards the end, is true of pronounced thyrotoxicosis. But even with this allowance, which often justifies itself, the values of radioiodine diagnosis frequently diverge from the clinical data (according to our observations jointly with Stegeman, in 16 per cent of the patients).

This is explained by the fact that both the onset of thyrotoxicosis and its severity do not always depend on the functional state of the thyroid and its hormonal activity, which are reflected in data of radioiodine diagnosis. Of great importance here is the reactivity of the organism, of its nervous system to the produced hormone. If the reactivity of the nervous system is for some reason elevated, then even the ordinary production of thyroxin might induce thyrotoxic phenomena. This is the case in the climacteric and pubescent age periods when the percentage of divergences, according to observations we conducted jointly with Stegeman, is from two to four times greater than usual. If the reactivity of the nervous system is reduced, even an excessive uptake of radioiodine and the concentration of thyroxin in the organism will not induce a thyrotoxic effect. This can be observed in persons who lived for a long time in an endemic goitre region, whose thyroid gland has preserved the capacity for greater uptake of iodine, notwithstanding the fact that they moved to a locality where there is sufficient iodine in the environment. It may also be assumed that in some cases the hyper- or hypofunction of the thyroid, revealed by radioiodine diagnosis, is a compensatory responsive reaction to the primary decreased or elevated reactivity of the organism to thyroxin.

Quite recently H. P. Higgins has reported the results of a study of the functional state of the thyroid in 333 patients with the aid of I^{131} introduced intravenously in a dose of 4-10 μC, with a check of radioidine uptake in

the course of 10 minutes. He assumes that this method makes it possible better to differentiate between the hyper- hypo- and the euthyroid conditions than by the methods used until now. But the dose of I^{131} recommended and the way it is administered may not be safe; therefore, the possibility of applying this method requires further study.

From all the aforesaid it follows that it is impossible faultlessly either to diagnose thyrotoxicosis or to judge its severity solely on the basis of the results of the accumulation of I^{131} by the thyroid. At the same time radioiodine diagnosis is of exceptional value: 1) in differentiating between thyrotoxic neurosis and neuroses of a general type; 2) in establishing the therapeutic dose of I^{131} for a thyrotoxic patient (which will be discussed later); 3) in evaluating the activity of antithyroid preparations, as rightly pointed out by Kopelovich and Draznin. Although the above considerations reduce to a certain extent the value of radioiodine diagnosis for differential diagnosis in thyrotoxicosis, nevertheless it has an advantage over the use of the basal metabolism rate for the same purpose. In contrast to the latter method, radioiodine diagnosis is not an indirect but a direct indicator of the functional state of the thyroid. Comparing these two methods of functional diagnosis of the thyroid gland, Draznin showed that in 34 out of 114 patients with an uptake of 60-80 per cent of I^{131} in 24 hours, i.e., with very high hormonal activity of the thyroid, the basal metabolism did not exceed +15 per cent and in three of them was below +10 per cent.

In thyrotoxicosis the activity of other endocrinal glands is also disturbed. We shall discuss only those whose change of function in thyrotoxicosis is manifested clinically in one or another way. These include the gonads and the adrenals in the first place. In thyrotoxicosis among women a number of investigators have established disturbances of the menstrual cycle and prolonged amenorrhea,

degenerative and atrophic alterations in the ovaries, atrophy of the womb and mammary glands, the falling out of pubic and axillary hair. According to data of the clinic *of the All-Union Institute of Experimental Endocrinology* (S. K. Lesnoy), alterations of the ovulatory-menstrual function (which appear at a certain time after the onset of thyrotoxicosis, or more seldom, simultaneously with it) are observed in 18 per cent of the women with thyrotoxicosis. In mild thyrotoxicosis they are seen in 10 per cent of the patients, in moderately severe thyrotoxicosis in 20 per cent, and in severe thyrotoxicosis in 25 per cent of the patients. Hypotrophy of the internal and external genitalia is noticed only in some patients with moderately severe thyrotoxicosis and more often, with severe thyrotoxicosis. At times in moderately severe and severe thyrotoxicosis the falling out of pubic and axillary hair is noticed. Lesnoy observed the complete falling out of these hair in two patients with severe thyrotoxicosis. A decrease of libido and potency among men and orgasm in women with severe thyrotoxicosis cannot be credited with certainty solely to thyrotoxicosis since the general grave condition of the patients may also play a part in it.

As seen from the above, in thyrotoxicosis of diverse severity the incretory function of the gonads and, consequently, the closely connected reproductive power is affected in a definite percentage of women. But the frequency of such disturbances even in severe thyrotoxicosis is relatively small and pregnancy and childbirth are still possible in the case of a substantial number of women.

Pregnancy, as pointed out earlier, may precede thyrotoxicosis as an aetiological factor.

In examining the connection between thyrotoxicosis and pregnancy a number of practically important questions arises. First, may pregnancy be allowed in the case of an enlarged thyroid and in thyrotoxicosis of diverse severity; second, are an enlarged thyroid and thyrotoxicosis an indication for an abortion; third, what should be

the medication measures in thyrotoxicosis in the period of pregnancy. Theoretical prerequisites and clinical observations suggest the following answers to these questions:

1. If there is an enlarged gland without thyrotoxic phenomena and if the gland for its size and location does not compress surrounding organs, pregnancy is allowed and, the more so, there are no grounds for an abortion. In these conditions pregnancy either does not affect the size of the thyroid and its function or induces such changes which disappear when pregnancy ends.

2. In mild thyrotoxicosis in women of a relatively young age it is advisable to avoid pregnancy until effective antithyroid treatment since pregnancy may exacerbate the thyrotoxicosis. In mild thyrotoxicosis the patient is usually treated during pregnancy as well; that is why in such cases there are no indications for an abortion, the more so since the latter might also affect the course of the thyrotoxicosis.

3. In severe thyrotoxicosis pregnancy is contraindicated and it is necessary to interrupt it because, under the influence of pregnancy, thyrotoxic phenomena are usually exacerbated.

4. In moderately severe thyrotoxicosis, just as in mild thyrotoxicosis, it is advisable to avoid pregnancy until preliminary antithyroid medication has been completed. The question of an abortion in such cases requires individual evaluation since in such a form of thyrotoxicosis both the continuation of pregnancy and its interruption equally entail the risk of causing an exacerbation. The mood of the patient is a decisive element. If the woman insists on continuing the pregnancy, this may be allowed; if she is apprehensive of an exacerbation of the disease, and is afraid of continuing the pregnancy or, if apart from thyrotoxicosis there are also other diseases, which by themselves are not sufficient indications for an abortion, pregnancy should be interrupted.

5. Thyrotoxicosis in pregnant women, if pregnancy is preserved, requires treatment throughout its duration. The use of methylthiouracil is contraindicated because of its toxic side effect, particularly on leucopoiesis and the possibly inhibiting influence, through the hypophysis, on embryonic growth. Microdoses of iodine are used according to the general principle (which will be discussed later). If, however, owing to the severity of thyrotoxicosis (in cases when the patient insists on preserving pregnancy), surgical intervention is needed, it is not contraindicated. At worst it can induce an abortion and at best, which is frequently the case, it rids the patient of thyrotoxic phenomena and ensures the normal continuation of pregnancy.

All the aforesaid about contraindications to pregnancy and indications for an abortion in thyrotoxicosis are merely a general scheme for guidance in which life introduced its endless adjustments that should be taken into account in settling a question of such importance for woman.

In pronounced thyrotoxicosis there are definite data pointing to adrenal cortex insufficiency. Possibly this is a result of the hyperfunction of the adrenal cortex arising at the initial stages of thyrotoxicosis which, as is known, is the case in any infection, intoxication and severe ailment. Among the symptoms of adrenal insufficiency in pronounced thyrotoxicosis are adynamia, blood vessel hypotonicity (low diastolic arterial pressure), frequent hyperplasia of the thymus and lymphatic system, a frequent thymicolymphatic state (the cause of sudden death in surgical intervention), lymphocytosis, melanoderma on spots characteristic of the bronzed skin disease. Of interest in this respect is the work now conducted at the All-Union Institute of Experimental Endocrinology (Y. Z. Gincherman) to determine in thyrotoxicosis the functional activity of the adrenals with the help of a urea-chloride-water index (the ratio of urea in the urine to urea in

the plasma, multiplied by the ratio of plasma chlorides to chlorides of the urine and by the ratio of the volume of the largest portion of urine eliminated in daytime after the water load to the volume of urine elimination at night). This method is based on the active participation of the adrenal cortex in regulating the protein and water-saline metabolism. A value of the urea-chloride-water index below 25 indicates functional adrenal cortex insufficiency. Measurement of this index in patients with thyrotoxicosis of different severity showed a lowered index in 48 per cent of the patients with moderately severe thyrotoxicosis and in 85 per cent of the patients with severe thyrotoxicosis.

Experimental thyrotoxicosis induces in the hypophysis an elevation of the eosinophilic cellular elements and a decrease of the basophilic cellular elements. Clinically, this is manifested in case of thyrotoxicosis, possibly, in more intensive growth of children and in retardation of the menarche. We pointed out earlier that in thyrotoxicosis anatomical and histological alterations have been observed in the pancreas and its insular apparatus, with the clinical picture of real pancreatic diabetes mellitus.

Thyrotoxicosis proceeds most frequently chronically, with periodic exacerbations and remissions. That is why evaluation of the working capacity of the thyrotoxic patient must vary in different periods of the disease. Severe thyrotoxicosis fully incapacitates the patient and frequently turns him mainly into a bedrid patient. Moderately severe thyrotoxicosis requires definite restrictions in the work usually performed (shorter working day, work at home, etc.). In mild thyrotoxicosis it is enough to free the patient from overtime work. In view of the role of the nervous system in the thyrotoxic process, night work, intensive manual and mental labour are contraindicated in all forms of thyrotoxicosis, including mild. This contraindication also holds good for periods of remission when the health of the patient seems to be fully restored.

It should be borne in mind that each neurosis (and thyrotoxicosis too is such to a certain extent, as pointed out earlier), according to the teaching of Pavlov, makes the nervous system especially susceptible to injury, and its higher parts particularly vulnerable to unconditioned and conditioned irritants of different nature.

Treatment

The modern conception of the role of the nervous system, of its higher parts in the genesis and course of thyrotoxicosis predetermines a number of measures designed to normalise this function. The most important aim to increase the inhibitory process in the cerebral cortex, proceeding from the premise that the pathological focus of excitation in the subcortical structures, which maintains the hyperfunction of the thyroid, depends on the predominance in the cortex of an irritation process irradiating into the subcortical region. But this is true only for some of the patients. In a definite state of the higher nervous activity the transmission of impulses from the cortex to subcortical centres proceeds by way of positive induction and then the pathological focus of excitation in the subcortical region might correspond to the prevalence of an inhibitory, and not an excitatory, process in the cortex. The measures designed to elevate the inhibitory state of the cortex in these conditions might worsen the condition of the patients, increasing the excitation of the subcortical structures and, correspondingly, the activity of the thyroid gland. It is not easy to determine in advance, before beginning treatment, the state of the higher nervous activity of the patient and it is not always possible to do it, the more so, since the instrumental, anamnestic and other methods used for this purpose give only an approximate idea of the state of cortical dynamics. That is why great caution must be exercised in any medication designed to combat the disease, thyrotoxicosis in the given case, and

to normalise the disturbed higher nervous activity, especially when it is impossible to investigate its state in advance. It is with this reservation that we begin the discussion of measures for elevating the inhibitory condition of the higher parts of the central nervous system in patients with thyrotoxicosis.

Here in the first place come bromides. Bromides have been used for a long time and readily in treating thyrotoxicosis in doses of 2-3 g daily, in expectation of their sedative action on the nervous system by easing the irritatory cortical process. Pavlov stressed that the action of bromide consists in increasing the inhibitory process in the cortex and that its dose should vary, depending on the type of higher nervous activity: the weaker the nervous type the smaller the dose of bromide should be; the gradation of effective doses of bromide is exceedingly great. In experiments on dogs the ranges of such doses were determined in a proportion of approximately 1,000 times (Pavlov); excessively large doses of bromide may do harm to the patient, and not good. All this makes it necessary before prescribing bromides in thyrotoxicosis to determine the type of higher nervous activity of the patient But in view of the difficulties this involves, it is necessary, without resorting to such a determination, to begin treatment with small doses, taking into consideration the fact that people with a weak type of higher nervous activity are the most susceptible to neuroses and, consequently, to thyrotoxicosis; only when the small doses produce no effect should one gradually go over to larger doses because representatives of the strong, particularly impetuous, type also become sick with neuroses, true, more seldom.

Practically, in the polyclinic of the All-Union Institute of Experimental Endocrinology (S. M. Brukman) treatment began with the prescription of bromides, 0.1 g daily (Sol. Natrii bromati 1% 200.0, one teaspoonful twice daily) with a gradual increase of the dose, in case of necessity,

up to 1.2 g daily (Sol. Natrii bromati 2% 200.0, one tablespoon three times daily). The effect was observed in mild thyrotoxicosis, especially in patients with a slightly enlarged thyroid and a clinical picture in which general neurotic phenomena predominated. In moderately severe and severe thyrotoxicosis the use of bromides alone produced no effect. In patients who were not relieved by bromides, the addition of caffeine in doses of from 0.02, to 0.1 g daily (in accordance with Pavlov's view about its action in neuroses) did not change the results of medication.

Rest was likened to bromides by Pavlov as regards efficacy in treating neuroses. This makes it necessary to approach very seriously the question of working out a regimen for a patient with thyrotoxicosis. If such a patient is employed, his work must be strictly regulated, without overtime, with the exact observance of the hours and days of rest and the use of this time for a real rest and not for any occupation. If the thyrotoxicosis becomes exacerbated, an interruption in work is obligatory. Patients must spend their holiday in the countryside. Their stay in sanatoria, holiday homes and health resorts, with many new impressions usual in such surroundings, might become a source of new irritating impulses for the thyrotoxic patient and worsen his condition. The special favourable effect on thyrotoxicosis, attributed to some health resorts, has not been justified in practice.

The desire to treat thyrotoxicosis by increasing the inhibitory process in the cerebral cortex naturally raises the question of applying sleep therapy. Sleep, according to Pavlov, is irradiated inhibition. Periodic sleep, as rightly pointed out by E. A. Asratyan, plays the part of protective inhibition. It protects in the first place the nerve cells of the cerebral cortex from exhaustion, which would set in if their excitation under the influence of various irritants in the waking state would not be replaced by inhibition during sleep.

The derangement in thyrotoxicosis of the normal correlation between processes of cortical excitation and inhibition usually leads to a disturbance of the normal alternation of periods of waking and sleep, which is most often manifested in insomnia. This is a direct threat to the cortical cells which are working at an overstrain. That is why the main task in treating thyrotoxicosis is to restore the patient's normal sleep, removing for this purpose the conditions which hamper the proper alternation of the waking state with sleep of sufficient duration. The patient must at once be released from night duties if they form part of his job. The hours of sleep must be strictly fixed and an atmosphere customary for normal sleep must be provided. Natural sleep must be achieved by all unconditioned and conditioned reflex measures of influence, including the use of somnifics.

But the treatment of thyrotoxicosis by prolonged or lengthy narcotic sleep must not be recommended for wide use. The organism is not indifferent to the large doses of somnifics needed for this purpose. They might adversely affect the functions of important organs, disturbing the course of metabolic processes in the organism and changing its immunobiological properties. So far there are no adequately substantiated theoretical and experimental data pertaining to the selection for this purpose of the most effective and least harmful somnifics, their dosage and depth of the sleep they induce (E A. Asratyan).

Physical therapy has been used for a long time in thyrotoxicosis. Its efficacy has been explained by the favourable action on the skin receptors and, in this way, on the vegetative nervous system. Preference has been given to water cure which exerts a sedative influence on the nervous system (cool baths and similar sponging, wrapping); objections have been raised to treatment accompanied by sharp mechanical or thermal action on the skin. Pavlov's physiological teaching necessitates a different approach

to both the explanation of the way physical therapy acts and the choice of the treatment.

The experiments of Pavlov, Bykov and their collaborators have demonstrated the direct conditioned reflex connection between the skin and the higher parts of the central nervous system. Proceeding from this, the assumption might be voiced that physical therapy with its chemical, electrical, mechanical and thermal factors, irritating the neuroreceptors of the skin, facilitates the formation in the higher part of the central nervous system of a new focus of excitation with phenomena of subsequent inductional inhibition (inhibition from negative induction) of the main pathological focus which maintains the thyrotoxicosis. It is this action evidently that comprises the therapeutic action of physical therapy in thyrotoxicosis.

The possibility of suppressing or ameliorating the pathological condition with the help of inductional inhibition in the higher part of the central nervous system has been demonstrated by A. O. Dolin and I. I. Zborovsky in experiments with camphoric epilepsy. They have also shown that in experimental conditions the one and the same irritant induces inductional inhibition, reduces the pilocarpine salivation in a dog of the weak type, but produces an opposite summational effect with greater salivation in a dog of the strong type. Hence preference should not be given to one type of treatment for all thyrotoxic patients. The choice of treatment requires individualisation. The success of physical therapy treatment depends upon able choice. The question of the mechanism of action of physical therapy requires further study.

The use of iodine and its preparations holds first place among measures designed directly to influence the hyperfunction of the thyroid in thyrotoxicosis. As shown by investigations with tracer iodine, a hyperfunctioning thyroid absorbs iodine entering the body much faster and more actively than a normal thyroid. In thyrotoxicosis the sensitivity of the thyroid to iodine, in whatever form and

in whatever way it is introduced, is especially great. An effect is produced by small doses which usually do not influence healthy people at all and have no reflection on their pulse rate, their weight or the basal metabolism. These doses are much smaller than those which may cause so-called Jod-Basedow. Small doses of potassium iodide, recommended by Neisser, amount in most cases to 0.0075 g three times a day. The doses proposed by Plummer—from one to 15 drops of the Lugol's solution three times a day—are large doses and exceed Neisser's doses many times over. With the special sensitivity of the organism to iodine they may cause severe phenomena of iodism and exacerbate the thyrotoxic process.

Various doses of iodine have been proposed for treating thyrotoxicosis, ranging usually between the Plummer and Neisser doses. Observations, conducted over many years in the clinic and polyclinic of the All-Union Institute of Experimental Endocrinology, have demonstrated in the case of tens of thousands of patients with thyrotoxicosis of varying severity the sufficient efficacy in light and, partly, in moderately severe thyrotoxicosis of doses of 0.0005-0.001 g of iodine and 0.005-0.01 g of potassium iodide daily, prescribed usually in pills or a mixture.

Rp. Jodi puri 0 02
Kalii jodati 0 2
Extr Valerianae 4 0
Massae pil ut fiat
pil N 40
S One pill twice daily

Rp Jodi puri 0 02
Kalii jodati 0 2
Aq destill 200 0
S One teaspoon twice daily

Potassium iodide alone is also prescribed in the form of a mixture in the indicated dose. The latter prescription is for patients in whom pure iodine leaves a bad taste in the mouth or causes nausea and vomiting. The administered iodides, in the opinion of various authors (N. P. Krav-

kov and others) act through the iodine released from them. The effect of microdoses of iodine, irrespective of the severity of the disease, tells already at the end of the first course of treatment in some patients and at times after two or three courses. But after each 20-day course an interval of a similar period is required since a refractory period to iodine usually appears in most patients in the process of treatment and its mollifying action on the thyrotoxic phenomena ceases. A three-week interval is approximately the period in which the afteraction of iodine is preserved and which is sufficient for restoring sensitivity to iodine. But in some patients already on the 7th-10th day of the interruption in iodine treatment thyrotoxic phenomena become aggravated and the interval between the courses of iodine therapy has to be shortened. At the same time there are thyrotoxic patients in whose case microdoses of iodine have no effect at all, or patients with particular sensitivity to iodine in whom even small doses of iodine induce acute phenomena of iodism in the form of a strong heart palpitation, diarrhea, headaches, salivation, lacrimation, etc. There are not many patients with these two types of reaction to iodine, but they are encountered nevertheless and iodine therapy in their case is either useless (patients of the first group) or impossible (patients of the second group). Here it is necessary to resort to other medication methods, which will be discussed subsequently.

Much attention has been given to the mechanism of the action of iodine in thyrotoxicosis. But to this day there is no full clarity on this question. Some explanations are directly opposite to each other. In the main, they all resolve to the point that the iodine introduced in the organism either prevents the formation of a normal molecule of thyroxin in the thyroid gland or, altering the structure of the colloid or the permeability of the tissues around it, hampers the passage of the hormone from the gland into the blood. There is also the supposition that iodine, de-

pressing the thyrotropic function of the hypophysis, inhibits the production of thyroxin by the thyroid.

The existing theories of the action of iodine in thyrotoxicosis cannot be considered satisfactory since they are of a hypothetical nature and absolutely do not explain why it is small doses of iodine that are effective. Some light on this point is shed by the statement of Pavlov about the different efficacy of large and small doses of bromide depending on the type of higher nervous activity. By analogy the following idea is suggested (so far only as a hypothesis): is not the action of iodine, like bromide, realised through the higher parts of the central nervous system and is not the efficacy of small doses explained by the fact that representatives of the weak type of higher nervous activity who react positively to small doses and negatively to large doses, are more susceptible to neuroses and, consequently, to thyrotoxicosis. The resistance of some patients to iodine possibly is explained by the nonconformity of the dose used to the type of higher nervous activity of the patient, inasmuch as people with a strong, particularly impetuous, type of higher nervous activity also suffer from thyrotoxicosis, just as from neuroses, true more seldom. That is why in the absence of effect from small doses of iodine the doctor possibly should not give up this form of medication, but should follow the line of gradually increasing the doses of iodine preparations. All this is expressed by way of a hypothesis so far and requires experimental confirmation.

The absence of a satisfactory explanation for the efficacy of microdoses of iodine and, owing to this, lack of confidence in the possibility of its independent action have prompted a number of authors (foreign in the first place) to recommend the use of iodine with narcotics (luminal) and cardiacs (digitalis) in order to expect more confidently the mollification of some thyrotoxic symptoms. We must object to such a wide employment of luminal and espe-

cially digitalis in all thyrotoxic patients without special indications for their use.

A good effect (slowing of the pulse rate, reduction of nervous excitation and the basal metabolism and a gain in weight) from the use of iodine alone, without adding other preparations, was seen by the authors who for the first time suggested the use of microdoses of iodine in thyrotoxicosis, and also in subsequent observations. This is also confirmed by our own numerous observations. The use of digitalis in thyrotoxicosis for the sole purpose of slowing the pulse rate is inadvisable. In addition to exciting the centre and the peripheral ends of the vagus, which essentially determines the effect of digitalis on cardiac slowing, digitalis also affects directly the myocardium (Kravkov and others), increasing cardiac contractions, the stroke volume and arterial pressure. This is an additional load for the heart, which is already working very intensively in thyrotoxicosis, and it may cause its premature insufficiency. Moreover, the slowing of cardiac contractions subsequently gives way to a faster rate of contractions owing to the excitation of the neuromuscular apparatus of the heart. Such an authoritative cardiologist as G. F. Lang writes: "Digitalis is powerless against tachycardia inherent in Basedow's disease". The prescription of small doses of digitalis (0.05 g daily) for a long time (20 days) does not always change the situation since, according to Lang, the response of the myocardium to digitalis is individual and the difference between its therapeutic and toxic doses is small; digitalis even in doses close to therapeutic may have a toxic effect on the myocardium. At the same time in thyrotoxicosis digitalis undoubtedly is an indispensable means in the early stages of the development of cardiac insufficiency and also of auricular fibrillation, in which digitalis inhibits the transmission of the impulses from the auricles to the ventricles. In these conditions the usual dose of digitalis (0.05-0.1 g two or three times a day) should be prescribed.

In his lectures on the therapy of Basedow's disease S. P. Botkin had the following to say about digitalis: "Digitalis has been, and is being, used here very frequently, but hardly many of those who prescribed it have grounds for saying anything good about it. . . . This is true in the first period of the disease—*Nota Bene*—when the heart beats are frequent and strong. In the second period, however, when the contractions of the heart are frequent but weak and compensation is disturbed, here you might get a benefit from digitalis, nevertheless the result will be by far not as splendid as in the case of ordinary vitium cordis. . . . Of this, I repeat, I have become convinced in a considerable number of patients and I have no doubt whatsoever on this point."

As for luminal, the reduction under its influence of the excitability of the subcortical centres and the cerebral cortex is beyond doubt. The use of luminal for this purpose is indicated in thyrotoxicosis, although not for all patients. Frequently in systematic treatment with luminal (for 20 days without interruption) even in small doses (0.02 g daily) patients complain of drowsiness, which it is hard to overcome even during work. Here evidently it is a case of patients with a prevalence of inhibitory reactions, just as it has also been observed in essential hypertension (A. L. Myasnikov). That is why we advise to prescribe luminal in usual doses only to thyrotoxic patients with excessive nervous excitation and who suffer from insomnia.

If there are real indications for the use of digitalis and luminal it is preferable to prescribe these remedies separately from the microdoses of iodine, not to include them in the iodine pills for the 20-day treatment course. This is dictated, first of all, by the consideration that the period of administration of digitalis and luminal are determined by the actual requirement in them and that these remedies must not be prescribed for 20 days in advance without control· secondly, it is inadvisable, without need, to lump

together in one prescription a number of preparations. It is in place here to recall the statement of Pavlov: "It always seemed strange to me when I saw a prescription with three and more therapeutic substances. What a dark hotchpodge this must be!"

The prescription of microdoses of bromide in the intervals between the iodine medication courses is a useful addition to microdoses of iodine in treating thyrotoxicosis. Microdoses of bromide intensify the results of treatment in the forms of thyrotoxicosis where the effect of iodine microdoses alone is inadequate. It is also advisable to prescribe simultaneously with the course of iodine microdoses, or in the intervals between them, courses of insulin treatment (10-15 days, 4-8 units daily) and intravenous injection of glucose (for the same period, 20 ml 40 per cent solution daily), especially in patients with noticeable exhaustion.

An organic compound of iodine, diiodotyrosine, is used quite widely for treating thyrotoxicosis together with inorganic iodine. It is an intermediary formation in the process of synthesis of thyroxin from iodine and protein in the thyroid gland. Diiodotyrosine can also be obtained synthetically. Some authors, without sufficient reason, regard this preparation as an antagonist of thyroxin and in this way explain its therapeutic effect in thyrotoxicosis. In the opinion of others, this preparation acts by means of the iodine it contains. Such a conception of its mechanism of action fully explains the smaller efficacy of diiodotyrosine, according to our observations, than inorganic iodine. The thyroid gland absorbs only iodides (Leblond, after A. T. Kameron) and therefore utilises only the iodine released from the organic compound of the introduced diiodotyrosine, while the rest of the bound iodine is excreted from the organism.

Diiodotyrosine is used in practically the same way as inorganic iodine. It is prescribed in doses of one tablet (0.05 g) twice daily for 20 days, with 10-20-day intervals

between courses. Some patients have a definite resistance to diiodotyrosine, just as to iodides. It is interesting to note, however, that frequently in the selfsame patients thyrotoxic phenomena respond well to treatment when diiodotyrosine is replaced by inorganic iodine. Evidently, it is a case not of the immunity of the organism to the iodine contained in diiodotyrosine (which is also possible), but of insufficient uptake by the thyroid of the iodine contained in the diiodotyrosine.

Thus, although diiodotyrosine has no advantages over inorganic iodine and its efficacy is even somewhat inferior, it nevertheless may be recommended for use in thyrotoxicosis. Prolonged repeated administration of iodine microdoses often becomes burdensome for patients, they are disappointed in the results of treatment and their mood is depressed; the replacement of one preparation by another, although similar in essence, favourably affects the mind of the patient, raises his spirits, which is very important for the success of treatment.

Thiourea derivates have been used for the treatment of thyrotoxicosis in recent years. The most widespread of them is 6-methylthiouracil which is less toxic than thiourea and its other derivates. The favourable action of these preparations is based on the fact that they inhibit the function of the thyroid gland, hampering the synthesis of thyroxin in it. The works of D. S. Tendler from the laboratory of E. Sh. Airapetyants have demonstrated the action of 6-methylthiouracil on the cerebral cortex; under its influence both excitatory and inhibitory cortical processes are relaxed.

Observations conducted for many years in the clinic (A. G. Vasilyeva) and polyclinic (N. S. Logotkina) of the All-Union Institute of Experimental Endocrinology have made it possible to establish precise indications for, and contraindications to, the use of 6-methylthiouracil. This preparation is very effective in all forms of thyrotoxicosis, including severe It is also effective in patients immune

to iodine microdoses. It is prescribed in a dose of 0.2 g thrice daily before amelioration of the thyrotoxic phenomena, then in a dose of 0.2 g twice daily until their substantial remission and, lastly, in a dose of 0.2 g daily until their complete disappearance (most frequently within 1.5-2 months after the ingestion of 25-30 g of the preparation); after this a maintenance dose of 6-methylthiouracil of 0.1-0.05 g daily is prescribed for 4-6 months. The full cessation of therapy following the disappearance of thyrotoxic phenomena, just as an interruption in its ingestion in the period of amelioration of the thyrotoxic phenomena, may lead to a new exacerbation of the pathological process. Since 6-methylthiouracil might cause a number of complications, at times rather severe, which will be discussed later, it should be used only when there is no hope of getting an effect with iodine microdoses usually safe as regards complications.

The gravest complications observed in the use of 6-methylthiouracil are leukopenia and granulopenia which might develop into agranulocytosis. The leukopenic reaction does not depend either on the severity of the thyrotoxicosis or the quantity of the administered preparation. That is why in prescribing 6-methylthouracil, it is necessary to study the blood of the patient both before the prescription of the preparation and throughout the entire period of its ingestion, including maintenance doses, not less than once in seven or ten days. A leucocyte count of about 4,000 and neutrophils of about 35 per cent are a contraindication to the prescription of 6-methylthiouracil and an indication for the cessation of therapy. Sometimes after a 5- or 7-day interval in the ingestion of 6-methylthiouracil the morphologic constituents of the blood become normal and stay within normal bounds throughout the period of ingestion of the preparation. If, however resumption of treatment with 6-methylthiouracil after a forced interval again affects the morphological constituents of the blood, it is necessary to discontinue its use. In such

patients pentoxyl and thesan produce a good effect in stimulating leucopoiesis, and Cortin is used successfully for influencing neutropenia and lymphocytosis.

Just like other related preparations, 6-methylthiouracil may cause, together with a decrease in the function of the thyroid, an enlargement of its size (so-called goitrogenous effect). So far there is no satisfactory explanation of this phenomenon. It, as some assume, represents a secondary reaction of the thyroid gland to the increased secretion of thyrotropin by the anterior lobe of the pituitary determined by the decreased concentration of thyroxin in the blood. Enlargement of the thyroid, notwithstanding the improvement of thyrotoxic phenomena, usually upsets the patient greatly. If the thyroid is enlarged considerably in a definite direction it may compress adjacent organs. If the thyroid has nodules, their growth is dangerous in the sense of malignisation, although methylthiouracil has a weaker effect on nodular goitre. The doctor must remember the possible complications in prescribing 6-methylthiouracil. According to experimental data of Y. M. Kabak and Y. B. Pavlova (morphological department of the All-Union Institute of Experimental Endocrinology), the goitrogenous effect of 6-methylthiouracil can be prevented by the simultaneous prescription of iodine microdoses. According to observations conducted in the clinic and polyclinic of the All-Union Institute of Experimental Endocrinology, when microdoses of iodine were prescribed together with 6-methylthiouracil in their usual amounts and the usual intervals, as a rule there was no enlargement of the thyroid and it even decreased in some patients. It is inadvisable to prescribe 6-methylthiouracil in nodular goitre without special need; in case of treatment the condition of the thyroid, especially its nodules, should be carefully watched.

Under the influence of 6-methylthiouracil the production of thyroxin may decrease to such an extent that a hypothyroid or even myxoedemous state might develop.

In the hypophysis (according to experimental data) changes are observed similar to those after thyroidectomy. The ingestion of 6-methylthiouracil may also induce gastro-intestinal disorders, muscular pains, and allergic manifestations (nettle-rash, exacerbation of bronchial asthma, etc.). That is why mention of such conditions in the anamnesis is a contraindication to the use of 6-methylthiouracil; the onset of these complications during treatment, just as an enlargement of the thyroid, notwithstanding the simultaneous ingestion of iodine microdoses, dictates a cessation of therapy, after which all these phenomena disappear without trace.

In prescribing simultaneously 6-methylthiouracil and iodine microdoses, we have now discontinued the inclusion of methylthiouracil in the iodine pills, as we had done at the beginning. There are sufficient reasons for this. In treatment with iodine microdoses intervals between courses are required, as we pointed out earlier, while in treatment with 6-methylthiouracil continuous medication is needed for the maintenance of a stable effect and such interruptions are impermissible. Treatment with 6-methylthiouracil dictates the need for constant control over the action of the preparation, whereas the iodine pills are prescribed for 20 days and their use requires no special control. Moreover, the usual dose of 6-methylthiouracil of 0.2 g daily given in the pills is insufficient in severe and moderately severe thyrotoxicosis. The complications we enumerated above, although somewhat more seldom, are nevertheless also observed in cases when small doses of 6-methylthiouracil are used. All this makes it necessary to recommend the prescription of 6-methylthiouracil, together with iodine microdoses, when there are corresponding indications in thyrotoxicosis, but in separate prescriptions. 6-methylthiouracil is prescribed for continuous treatment, according to the scheme given above, while iodine microdoses are administered simultaneously in pills with the usual intervals.

Treatment with 6-methylthiouracil is not recommended in periods of the organism's growth (according to experimental and clinical data, it retards growth and physical development), during pregnancy and in diseases of the liver and kidney. In contrast to iodine microdoses, the use of 6-methylthiouracil is not indicated for preoperative preparation since, according to observations of the surgical department of the All-Union Institute of Experimental Endocrinology (O. V. Nikolayev), it raises the bleeding of the surgical wound. 6-methylthiouracil may be used in the preoperative period only in cases of severe thyrotoxicosis when the thyrotoxic phenomena cannot be ameliorated by iodine microdoses alone.

In conclusion it must me said that although 6-methylthiouracil is more effective than iodine and more often leads to a complete disappearance of thyrotoxic phenomena and for a longer period, its use nevertheless does not always guarantee against subsequent exacerbation. Moreover, there are patients resistant to this preparation.

A new preparation, mercazole (1-methyl-2-mercaptoimidazole), has been used lately for the chemical inhibition of the thyroid function in thyrotoxicosis. The principle of its application is the same as of 6-methylthiouracil. Treatment begins with 0.03 mg daily perorally (one tablet contains 0.005 mg of the preparation) until the amelioration of the thyrotoxic phenomena: then as the condition of the patient improves the dose is gradually reduced until the complete remission of the thyrotoxic phenomena. The last dose, 0.005 mg every other day is a maintenance dose. The general period of treatment (together with the maintenance dose) is from 4 to 5 months. The observations conducted so far at the All-Union Institute of Experimental Endocrinology show that mercazole, not inferior in efficacy to 6-methylthiouracil, acts more mildly and does not produce the complications inherent in the latter. Neutropenia, noticed in some patients, was not stable; the blood was usually normalised without additional measures

in a few days after the cessation of therapy; after medication was resumed complications as regards the blood did not recur in most cases. The indications for, and contraindications to, the use of mercazole are the same as for 6-methylthiouracil.

Roentgenotherapy, radioiodine therapy and surgical intervention are among the more radical measures in treating thyrotoxicosis designed to reduce the production of thyroxin by directly influencing the tissue of the thyroid. Roentgenisation of the thyroid in an experiment (according to data of A. M. Yugenburg and B. M. Shlepakova), eliminates the changes in thyroid tissue discovered in histological studies and the hyperthyroid phenomena which are induced in dogs after prolonged administration of thyroidin. Numerous clinical observations also point to a favourable action of roentgenotherapy, under the influence of which symptoms of thyrotoxicosis disappear or are considerably ameliorated in a number of patients. According to data of many authors, a positive effect is seen in 50 per cent of the patients. This percentage is even higher according to data of the clinic and polyclinic of the All-Union Institute of Experimental Endocrinology (Y. Z. Gincherman and B. M. Ioffe). According to these data, the severity of thyrotoxicosis has little influence on the ultimate results of the therapy, but it is reflected in the number of roentgenisation courses needed to obtain a positive effect: the more severe the thyrotoxicosis the more courses are needed. The biggest number of courses used by the authors was four. A course consisted of 6 treatments, with intervals of 1-2 days, and was repeated every 1.5-2 months. The thyroid gland was irradiated from two fields—from the right and the left. A single dose was 75 r, the general dose per field was 225 r and for the course, 400-450 r.

Almost a similar effect in thyrotoxicosis was seen in the clinic and polyclinic of the All-Union Institute of Experimental Endocrinology (the same authors) from roent-

genisation of the intermediary-pituitary region and the cervical sympathetic ganglions and also different parts of the skull, respectively the frontal-sincipital and the temporal-sincipital regions of the cerebrum. The authors used a course consisting of seven treatments, with intervals of from three to five days, one treatment each for the two temporal-sincipital regions and the frontal-sincipital region and two treatments each for both cervical sympathetic ganglions. The dose was 60-120 r per treatment and 420-820 r for a course. The obtained effect from roentgenotherapy in thyrotoxicosis furnishes grounds for the assumption that the action of roentgen rays on the thyroid gland in this disease is exerted (as in all forms of radiation) not only through direct influence on the tissue of the thyroid, but also through the central nervous system and the neuroreceptoral apparatus of the thyroid. The influence of roentgen rays on the functional state of the cerebral cortex has been demonstrated by M. I. Nemenov in the laboratory of Pavlov, in experiments with the conditioned reflex activity of dogs subjected to roentgenisation of different regions of the cerebrum.

The above methods of using roentgen rays in the ordinary dosage have proved ineffective or even harmful in a number of thyrotoxic patients; in such cases thyrotoxic phenomena are intensified or they are replaced by symptoms of hypothyroidism or even myxoedema. This is explained by the fact that the sensitivity to roentgen rays is individual and the therapeutic dose might be insufficient for some patients, while for others it might stimulate or inhibit the function of the thyroid gland. This limits the possibility of using roentgenotherapy in thyrotoxicosis and it should be applied only if there are definite indications.

In the opinion of a number of authors to which we subscribe, the following are indications for roentgenotherapy in thyrotoxicosis: 1) absence of effect from medica-

mentous treatment in pronounced forms of thyrotoxicosis and unwillingness of the patient to undergo an operation; 2) general severe condition of the patient, including pronounced alterations of the cardiovascular system when there is no confidence in a favourable outcome of surgical intervention; here we must make the reservation that cardiovascular insufficiency of thyrotoxic origin, even if it is sharply pronounced, is not a contraindication to an operation; on the contrary, according to our data, only timely surgical intervention can restore the normal cardiovascular activity; 3) postoperative relapses of the thyrotoxic goitre, particularly repeated ones; 4) for cerebral roentgenisation—pronounced general neurotic, including thyrotoxic, symptoms, with a small enlargement of the thyroid and the absence of effect from medicamentous treatment.

We cannot agree with authors who recommend roentgenotherapy in any form of thyrotoxicosis in the case of children and adolescents in the pubescent period. According to our observations, pubertal thyrotoxicosis, not sharply pronounced, either passes with age without any intervention, or responds well to iodine-bromide therapy; roentgenotherapy is not needed. Severe thyrotoxicosis in children when there is no effect from medicamentous treatment requires surgical intervention which children usually stand well. The indications for roentgenotherapy of severe thyrotoxicosis in children and adolescents are the same as for adults, only here special caution is required in view of the undoubted influence of roentgenisation on the nervous system which is especially labile at this age.

Another method of radiation therapy—treatment with radioactive iodine (I^{131})—is also now employed in thyrotoxicosis. This form of therapy is based on the principle that in thyrotoxicosis, owing to the swift and high uptake of the iodine entering the organism (3-4.5 times greater than the norm), a radioactive depot is formed in the thyroid, which becomes a source of internal beta radiation

of the tissues of the gland, exerting an inhibiting influence on its function. The small radius of action of the beta rays (about 2 mm) eliminates the possibility of harmful influence on organs and tissues adjacent to the thyroid.

In treating thyrotoxicosis with I^{131} the main question is its total dosage and the method of its administration—in single or divided dose. A number of authors, primarily foreign, recommend single large doses. Thus, Jaimet applied single doses of 10 mC; Larson, up to 20 mC; Cargil, up to 25 mC; Plamandon, up to 27 mC. Of Soviet authors, A. A. Atabek used a single large dose of 16 mC, basing such a method of treatment with I^{131} on data obtained experimentally on male rats whose thyroid tissue was fully destroyed after receiving 800 μC and even 200 μC; in a divided dose (each 5-7 days) the action of the first dose (800 μC) was much weaker, while the second dose had no effect whatever. In our opinion, these data speak not in favour, but against the application of large single doses. As will be shown later, the choice of one or another therapeutic dose is based on rather shaky grounds and the established initial dose is only a preliminary one. The finest calculations cannot determine precisely the necessary dose also because the sensitivity of the gland tissue to radial energy is extremely individual and cannot be established beforehand. According to data of Seed and Jaffe, in some patients a dose of 3 mC might induce hypothyroidism, while in others even a dose of 90 mC fails to effect a cure. That is why we are never confident that the administered dose of I^{131} is not excessive for the thyroid gland. Only a division of the dose can mollify its harmful action on the tissue of the thyroid, as seen from the experiment of Atabek. This does not change noticeably the general efficacy of radioiodine therapy, which is demonstrated by a comparison of the results of treatment with a single large and divided moderate dose, as will be described subsequently. In the latter method the action on the thyroid tissue, most likely,

is milder and more gradual. The dose which, when divided in the experiment of Atabek, did not exert any action on the thyroid tissue 22 days after the end of the experiment (52 days from its beginning) possibly would prove effective under more prolonged observations.

The great majority of Russian endocrinologists (V. K. Modestov and V. R. Klyachko, M. A. Kopelovich, N. V. Romashkan, I. I. Lyubskaya, N. M. Draznin and others) are in favour of treating thyrotoxicosis with small and moderate summary doses of radioiodine—from 3-4 to 8-10 mC, depending on the severity of the disease, the size of the thyroid and the degree of uptake of the tracer dose. Modestov and Klyachko introduce a summary dose of 1-2 mC weekly; other authors, 2-4 mC, every 5-6 days. In dividing the summary dose of a course, equal parts are usually introduced in each ingestion or at first large doses are used and then smaller ones. According to observations of the clinic of the All-Union Institute of Experimental Endocrinology (Lyubskaya), the excretion of I^{131} in the urine after the introduction of repeated divided doses increases 1.5-2 times; consequently, the assimilation of radioiodine by the thyroid during its repeated administration decreases. If these data are subsequently confirmed, treatment should begin with smaller divided doses and end with larger ones.

The designated dose is swallowed perorally in 30 to 50 ml of water in a fasting state two hours before eating. For a month (according to data of Fairley, for six weeks) after the ingestion of I^{131} patients were not allowed to eat iodine-rich food or medicines containing iodine and bromide capable of dislodging I^{131} from the thyroid and thereby reducing its efficacy. All authors point out that even prior to administering a therapeutic dose of I^{131} patients should not be given medicines containing iodine and bromides for a certain period. Most authors set a period of one month for iodine and bromide preparations (Kopelovich and Foteyeva, a period of 1.5 to 2 months);

for other antithyroid preparations this period is cut by different authors to two weeks, to 10, 4 and even 2 days.

The interruption in antithyroid medication, recommended prior to I^{131} therapy, is designed to elevate the ability of the thyroid to accumulate the therapeutic dose of I^{131}. Thus, it may be assumed that the longer this recess, the better for the patient. But we must not forget that frequently the condition of the patient is such that radical treatment brooks no delay and it is impossible to leave such patients without antithyroid medication for a long time. That is why this interval in treatment must not be too long. We believe that a monthly interval for iodine and bromide preparations and a two-week interval for other antithyroid remedies is quite sufficient, all the more since prior to the prescription of a therapeutic dose of I^{131} the iodine-accumulating function of the thyroid is checked with the help of the tracer dose.

The observations of Lyubskaya in the clinic of the All-Union Institute of Experimental Endocrinology are of interest in this respect. A therapeutic dose of I^{131} was given to three patients with severe thyrotoxicosis three weeks, seven and five days after the end of iodine therapy. All of them, according to data of radioiodine diagnostics, had a high degree of I^{131} uptake. All the patients in the course of 3 days, excreted in the urine only 10 per cent of the administered I^{131}, which speaks of an exceptionally good absorption of this radioisotope by the thyroid. From this it follows that in the case of patients with severe thyrotoxicosis who have urgent indications for radioiodine therapy and a sufficiently high iodine-accumulating function of the thyroid, I^{131} treatment may be started regardless of the brief period which passed since the discontinuation of iodine and other antithyroid medication. This question is of practical importance and requires serious study. To elevate the ability of the thyroid to absorb I^{131}, which is reduced after prolonged antithyroid medication, N. V. Ro-

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not ignore the severity of thyrotoxicosis and the iodine-trapping ability of the thyroid. A doctor should bear in mind that all these indications of the therapeutic doses of I^{131}, established according to the above methods, are only of relative and not absolute significance.

The action of radioiodine therapy is not felt at once but after a certain time upon its completion and is usually manifested only very gradually. The improvement in the condition of the patient becomes noticeable in the third or fourth week of treatment and is fully evident after two or three months. Amelioration of thyrotoxic phenomena at later dates is more seldom. Their full remission drags out for many months. The action in the main depends on the thyroid's power of resistance to the damaging effect of radial energy. This reaction of the thyroid to I^{131} is extremely individual and cannot be taken into account in advance.

Hence it is difficult to determine the indications for a repeated course of treatment if the preceding course did not produce a noticeable improvement in the usual period. We have recently seen a patient who was prescribed a second course of radioiodine therapy three months after the first course, since it had given no results. But owing to family circumstances she could not undergo it. When this patient came for an examination six months after the end of the first course, thyrotoxic phenomena were completely absent, although during this period she had received no antithyroid medication at all. Notwithstanding such delayed action of radioiodine therapy in some patients, one should not wait for results of treatment in severe forms for more than three months because in most cases this period is sufficient for revealing the action of I^{131}. If after three months an effect is totally lacking, the repeated dosage is increased; in case of a partial effect it is reduced by 25-50 per cent.

The results of radioiodine therapy are highly favourable. They have been observed approximately in 80-90 per

Fig 10 Patient, age 28, with moderately severe thyrotoxicosis Diffuse enlargement of the thyroid III degree Uptake of tracer dose of radioiodine after 2 hours, 34 3 per cent, after 4 hours, 42 8 per cent, after 24 hours, 47 8 per cent

Fig 11 Same patient three months after radioiodine therapy No thyrotoxic phenomena Thyroid enlargement reduced to II degree, working capacity restored (two years later general condition was similarly satisfactory, only a somewhat enlarged isthmus of the thyroid was palpable)

cent of the patients, with a complete remission of thyrotoxic phenomena in the greater majority of cases (Fig. 10, 11, 12, 13). Thus, according to aggregate statistics of American, British and French clinics (2,000 patients) cited by Atabek, thyrotoxicosis was cured in 86 per cent of the patients, according to summary data of 43 Soviet and foreign authors (5,380 patients), cited by Klyachko, remission after radioiodine therapy was observed in 79.6 per cent of the patients; according to summary statistics of Berthaux, Colas-Belcour, Lemarchal and Vignalou dealing with 5,550 patients, complete cure was registered in 74-92 per cent. The percentage of positive results ranges

approximately within the same bounds in the figures given by some Soviet and foreign authors. According to data of G. F. Blagman, R. A. Dymshitz, N. A. Grachova, V. S. Zudina and A. I. Strukova, it was 93 per cent; N. V. Romashkan, 94 per cent; A. A. Atabek, 97 per cent; N. M. Draznin, 97 per cent; Fauvert, de Genne, Cocovinis, 79 per cent; Plamandon, 91.6 per cent; according to data of the clinic of the All-Union Institute of Experimental Endocrinology (I. I. Lyubskaya), 85.3 per cent.

The influence of radioiodine therapy on exophthalmos is of interest. Some authors point out that it increases under the influence of I^{131}. Of Soviet authors N. V. Ro-

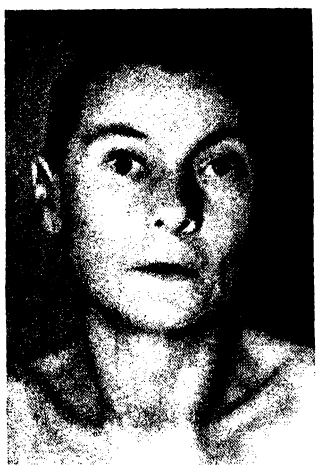

Fig 12. Patient, age 42, with severe thyrotoxicosis Diffuse enlargement of the thyroid III degree Uptake of tracer dose of radioiodine after 2 hours, 41 6 per cent, after 4 hours, 46 9 per cent, after 24 hours, 47 6 per cent

Fig 13 Same patient six months after radioiodine therapy. No thyrotoxic phenomena, usual weight and normal working capacity. The thyroid decreased in size considerably. Uptake of tracer dose of radioiodine after 2 hours, 7 per cent, after 4 hours, 10 8 per cent, after 24 hours, 19 9 per cent

mashkan drew attention to this point. Thus, of the 84 thyrotoxic patients with exophthalmos under his observation, the exophthalmos of 12 per cent of the patients increased after I^{131} therapy. Clark, Rule, Tripel, Cofrin and others therefore, hold that pronounced exophthalmos is a contraindication to radioiodine therapy. Most of the authors, however, have not observed an increase of exophthalmos under the influence of radioiodine therapy. On the contrary, in most patients the exophthalmos either disappeared or decreased considerably. According to data of Blagman and his collaborators, of 54 patients with exophthalmos, the latter completely disappeared or decreased substantially in 87 per cent and did not change in 13 per cent of the patients. In the observations conducted by Romashkan, an increase of the exophthalmos occurred in 12 per cent of the patients, it fully disappeared in 55 per cent and remained without change in 33 per cent. The favourable action of radioiodine therapy on exophthalmos is also mentioned by Klyachko, Atabek and others; to achieve such an effect a more or less long period is required, but it is shorter than after surgical intervention.

An increase of exophthalmos or its preservation without change in part of the patients after radiation or surgical treatment is explained by the fact that of all the thyrotoxic symptoms only the exophthalmos is directly dependent on the thyrotropic hormone of the hypophysis. Experimentally an exophthalmos can be induced by the administration of the thyrotropic, but not the thyroid hormone. According to data of B. V. Alyoshin and Y. E. Livergant, exophthalmic thyrotoxicosis differs from anexophthalmic by the degree of participation of the thyrotropic hormone in the process. In exophthalmic thyrotoxicosis, according to data of Livergant, the quantity of thyrotropic hormone in the blood is elevated or is normal (in anexophthalmic thyrotoxicosis the thyrotropic hormone is not found or its quantity is below normal). But in response

to the decrease of the concentration of the thyroid hormone in the organism after an operation or radioiodine therapy, there rises considerably the production of the thyrotropic hormone which maintains or even increases the exophthalmos. The more rapid subsequent disappearance of the postradiation exophthalmos as compared with the postoperative exophthalmos is explained, possibly, by the partial action of the ionising radiation on the hypophysis and its thyrotropic function.

The thyroid progressively decreases under the influence of radioiodine therapy. Usually this becomes noticeable already at the end of the first month of treatment, while after three to six months the thyroid either reaches a normal size or still remains somewhat enlarged. Favourable results of radioiodine therapy, followed up in a number of patients for several years, are stable. Relapses have been noticed in 0.5-2.3 per cent of the patients, according to data of different authors (Clark, Seed and Jaffe). We have not seen any relapses.

The exceptional efficacy of radioiodine therapy in thyrotoxicosis has won many proponents for this method of treatment. Some endocrinologists have begun to use it widely both in mild thyrotoxicosis and in thyrotoxicosis of moderate severity, without an attempt to treat the disease by other antithyroid means. To this we cannot agree. The I^{131} which gets into the organism is not only accumulated by the thyroid and excreted in the urine, but a certain part of it is also absorbed by other organs and tissues, including internal secretion glands, mainly the ovaries, hypophysis and adrenals. True, the concentration of I^{131} in these organs is small and no direct harmful effect on them during the use of therapeutic doses of this radioisotope has been observed in the clinic. But sensitivity to radiation action is individual and it might be elevated in one or another organ. This might have an especially negative effect in thyrotoxicosis not strongly pronounced when the uptake of I^{131} by the thyroid is

not so high and this may lead to its greater concentration in other organs, mainly those indicated above, with all the consequences following therefrom, which may be not immediate but distant. When these consequences develop gradually it is not always possible to trace their connection with the factor that caused them.

That is why we have to object to the use of radioiodine therapy when there is no special need for it. It should be employed, as is practised by most endocrinologists, only in severe thyrotoxicosis and the forms of thyrotoxicosis of moderate severity which do not respond to other antithyroid medication, i.e., only when it is impossible to achieve success by means designed solely to inhibit the function of the thyroid, whereas partial destruction of the gland tissue itself is required. Consequently, the general indications for radioiodine therapy must be similar to those for surgical intervention. Both these methods of treatment are radical. Can we regard them as rival methods, as some authors think, expounding the advantages of one or another of them? Of course, not. Both have their positive and negative aspects and, therefore, their special indications and contraindications and the two methods supplement each other well. Here we will discuss only the indications for, and contraindications to, radioiodine therapy, since questions of surgical treatment of thyrotoxicosis are examined in a special chapter. But it is understood that if radical treatment is needed the special indications for one of these methods are at the same time the contraindications for the other, and vice versa.

Radioiodine therapy is the only acceptable method of treatment when the patient is afraid of an operation and categorically refuses it. And this is not only because it is impossible to operate the patient against his will, but also because the sentiment of the patient against surgical intervention, his disturbed mental condition prior and during the operation may adversely affect its outcome.

Radioiodine therapy is particularly indicated in thyrotoxicosis accompanied by severe visceral alterations, particularly of the cardiovascular system, which cast doubt on the favourable outcome of surgical intervention. Patients with cardiovascular insufficiency (during the normal function of the thyroid) stand well even large single doses of I^{131} (up to 20-25 mC) used by foreign clinicists with the object of inhibiting the function of the thyroid and thus reducing the level of metabolic processes in the organism and the load on the heart. In such treatment one or another degree of improvement of cardiovascular phenomena has been noticed (according to the data of Harper, Brown and La Motte in 65.6 per cent of the patients, and according to the data of Blumgart, Freedberg and Kurland, in 68 per cent).

Radioiodine therapy is also indicated for patients in a thymicolymphatic state who can hardly undergo any surgical intervention and are threatened with sudden death during the operation. According to contemporary conceptions, the thymicolymphatic state is associated with the insufficiency of the adrenals; able use of corticosteroid preparations prior, during and after the operation can to a certain extent prevent an adverse reaction of these patients to the operation.

Radioiodine therapy is primarily indicated in relapsing thyrotoxic strumas, especially repeated ones (Fig. 14, 15). First, because the many commissures and concretions make repeated surgical intervention extremely difficult; second, possibly because after subtotal strumectomy the remaining part of the thyroid can preserve its full activity, including the tendency to intensive growth, while I^{131} destroying part of the thyroid evidently weakens at the same time the regenerative capacity of its remaining part as well. This, presumably, explains the extremely rare occurrence of relapses after radioiodine therapy. If an operation has had no effect, this is an indication for radioiodine therapy. We mean not relapses following the

Fig 14 Patient age 48, with severe thyrotoxicosis Diffuse enlargement of the thyroid III degree (relapse after struma ectomy) Uptake of tracer dose of radioiodine after 2 hours, 40 5 per cent after 4 hours 44 per cent after 24 hours 45 1 per cent

Fig 15 Same patient six months after radioiodine therapy No thyrotoxic phenomena except eye symptoms Only a somewhat enlarged isthmus of the thyroid is palpable Uptake of tracer dose of radioiodine is normal

temporary postoperative effect but the complete ineffectiveness of the operation

Insufficient iodine-accumulating ability of the thyroic in pronounced thyrotoxicosis is a contraindication to radioiodine therapy We pointed out earlier that such a nonconformity occurs and mentioned the reasons for it In these conditions the effect of radioiodine on the thyroic is doubtful, while the higher concentration of radioiodine in other organs and tissues is very probable

Radioiodine therapy must not be employed in urgent and the more so, vital indications for radical treatment in cases of extreme severity of the thyrotoxicosis or the

stenotic action of a retrosternal goitre, since radioiodine therapy, as pointed out above, produces an effect not before two or four weeks. Radioiodine therapy is contraindicated during pregnancy, beginning with the third month, in view of the possible adverse effect of I^{131} on the thyroid of the fetus with all the consequences for its growth and development. Radioactive iodine may pass with the milk into the organism of the child, therefore it also must not be used in the period of lactation and feeding the infant with mother's milk.

Radioiodine therapy in thyrotoxic nodular goitres remains a debatable question so far. According to data of all authors, the nodules of the thyroid respond harder to the action of I^{131}; the effect is obtained in a much smaller number of patients and doses 1.5-2 times larger than usual are required. Some authors (Atabek and Jaimet) do not rule out the possibility of using I^{131} in nodular goitre; others (Lyubskaya, Klyachko, Nikolayev, Berthaux, Chapman) object to this, considering that radioiodine therapy might serve as the direct impulse for the malignant degeneration of the nodule; moreover, with the tendency of nodules to malignisation, we must not replace the absolutely effective surgical method by the less reliable radiation treatment. We too are inclined to support this viewpoint.

Nor is there unanimity concerning radioiodine therapy of thyrotoxicosis in children and adolescents. Some authors (Blagman, Romashkan) make no distinction between patients as to age in this respect. Atabek holds that patients of a young age, all other conditions being equal, need even bigger doses of I^{131} owing to the higher resistance of the thyroid to it. On the other hand, Berthaux, Klyachko and others believe that radioiodine therapy is contraindicated for children and adolescents. The latter viewpoint, in our opinion, is correct. The thyroid plays an exceedingly important part in the physical, sexual and mental development of the child. The manifesta-

tions of congenital or early underdevelopment of the thyroid are very severe. That is why in the period of the organism's growth and development the use of ionising radiation, the destructive force of which cannot be exactly taken into account in advance, is extremely risky, the more so since children and adolescents stand surgical intervention not worse than adults, while postoperative hypothyroidism is observed much more seldom, evidently owing to the particularly good regenerative capacity of the thyroid at this age.

Hypothyroidism holds a big place among complications in radioiodine therapy. Radiation hypothyroidism is manifested much later than postoperative hypothyroidism and develops more gradually, which corresponds to the different mechanism of action of these two forms of radical treatment. Owing to this feature of radiation hypothyroidism, it might be overlooked in the initial period of its development and the moment might be missed when its treatment is most effective. This must be borne in mind. The absence of hypothyroidism shortly after the administration of I^{131} does not preclude the possibility of its subsequent onset and the patient which received radioiodine must be kept under prolonged observation.

According to data of various Soviet and foreign authors, hypothyroidism develops 2, 4, 6 and 12 months after the administration of I^{131} (Klyachko, Lyubskaya, Jaimet, Fairley), and according to the observations of Chapman, four years and even eight years later. Postradiation hypothyroidism may be transient, but it can also be stable and respond only to systematic treatment with thyroidin. The frequency of hypothyroidism in radioiodine therapy differs, according to data of various authors: from 3 per cent (Plamandon, Fairley) and 9 per cent (summary statistics of Klyachko and Cargil) up to 21 per cent (Chapman and collaborators) and even 24 per cent (Freedberg). A direct connection between the frequency of hypothyroidism, on the one hand, and the dose of I^{131}

and the method of its administration, on the other, does not always exist. The sensitivity of the thyroid to I^{131} is of great importance here, nevertheless, a number of authors (Jaimet and others) point out that large single doses lead more frequently to hypothyroidism. This is one of the serious arguments in favour of treatment with divided doses.

An exacerbation of the process in radioiodine therapy is observed in a number of patients with thyrotoxicosis, especially during its severe course. Such a phenomenon is seen in 5-10 per cent of the patients and this percentage is higher if account is taken of the appearance of some indistinct thyrotoxic symptoms. According to data of the clinic of the All-Union Institute of Experimental Endocrinology (Lyubskaya), it reaches up to 34.5 per cent. Real thyrotoxic storms, at times resulting in death, have also been observed. Lyubskaya found 8 such cases described in the literature at her disposal between 1950 and 1958. In all these patients prior to treatment the thyrotoxicosis had proceeded with severe cardiovascular phenomena. This dictates particular caution in treating such patients with radioiodine and division of the summary dose is particularly indicated. Jaimet rightly points to this and Berthaux is wrong advising to use substantial doses of I^{131} in cardiac complications of thyrotoxicosis in order to increase the chances of cure. He does not take into account the fact that in such patients large doses of radioiodine increase the chances of thyrotoxic storm, especially dangerous for them. In contrast to hypothyroidism, the exacerbation of thyrotoxicosis is most frequently noticed in the first days after the administration of radioiodine and usually passes after a certain time without any treatment or (if the thyrotoxic phenomena are strongly pronounced) under the influence of a bedfast regimen and symptomatic measures. Preparations of iodine and bromide are contraindicated since they might obliterate the action of radioiodine.

The cause of exacerbation of thyrotoxicosis during its radical treatment by radiation methods and more seldom by surgical methods remains a moot point so far.

While the exacerbation of thyrotoxicosis in the first days after an operation may be regarded as a result of the surplus influx of thyroxin into the organism in view of the manipulation on the thyroid, such an explanation is absolutely inapplicable either to the later postoperative or to the radiation exacerbation. It is more likely that in both cases the exacerbation of the thyrotoxicosis is caused by the excessive activation of the part of the thyroid preserved after the operation or the thyroid not yet damaged by the action of ionising radiation in response to radical intervention.

The influence of therapeutic doses of I^{131} on haemapoiesis and consequently on the composition of the peripheral blood could not escape the attention of investigators because it is known that in radiation sickness changes in the blood are manifested very early. Soviet authors pay special attention to this question. Some of them (Klyachko, Atabek) did not observe any noticeable changes in the peripheral blood even in large single doses, others (Kopelovich, Draznin and Chernova) saw mild changes in the morphological picture of the blood in radioiodine therapy. Different data have been obtained in the clinic of the All-Union Institute of Experimental Endocrinology (Lyubskaya) in the study of the peripheral blood of patients each 2-3 days and in part of the patients daily for 5-9 days after the administration of each divided dose of radioiodine (2-4 mC). There were no essential changes in the red blood. But leukopenia (below 4,000) and granulocytopenia (below 40 per cent) was seen in 32 per cent of the patients; in 12 per cent, pentoxyl and cortin had to be used for a long time to normalise the blood (cortin was given in cases when pentoxyl was ineffective). In half of the studied patients who were treated with radioiodine the number of thrombocytes

was reduced (in one patient less than 25,000). Thrombocytopenia was eliminated and prevented with the aid of cortin. It follows from these observations that substantial changes in the peripheral blood, noticed prior to the prescription of radioiodine therapy, are contraindications to its use and must be eliminated before treatment begins.

The question of possible immediate or distant cancerigenic action of radioiodine therapy is of special importance. This question arose after the communication by Goldberg and Chaikoff that malignant tumours of the thyroid appeared in rats 1.5-2 years after the administration of radioactive iodine. But numerous clinical observations in the course of 10-15 years, conducted by different investigators with different dosage of radioiodine, have not confirmed its cancerigenic action. That is why some authors fully rule out such danger in treating people with this isotope (Blagman and collaborators, Bowers) and they explain the divergence between the experiment and the clinic by the fact that the biggest clinical dose is but a tiny fraction of the dose used in the experiments. But other, more cautious endocrinologists introduce definite age limitations in the indications for the use of I^{131}. Most of them allow the use of radioiodine only in patients of an advanced age, whose remaining life span is within physiological bounds shorter than the periods tested for the possibility of postradiation malignisation. Others, on the contrary, doubt the safety of administering I^{131} after 40 years when the tendency towards malignisation in the organism rises. Taking into account all the aforesaid, we believe that when there are unconditional indications for radioiodine therapy (we pointed out earlier that only in these cases should it be used) apprehensions about its possible malignising effect should not be taken into account, the more so, in treatment with divided doses.

We shall not discuss rare and unstable complications of radioiodine therapy (skin itch, dyspeptic phenomena,

etc.). They pass without special medication and usually do not upset the main plan of treatment.

We have already discussed the regimen of the patient with thyrotoxicosis in the section on working capacity. We should add that prolonged stay and overheating in the sun and also any thermotherapy are contraindicated for patients with thyrotoxicosis in all its forms. Thermotherapy may be allowed under the control of a doctor in mild thyrotoxicosis if there are special serious indications for it (severe gynaecological diseases, cholelithiasis, etc).

Patients with thyrotoxicosis need no special diet. The old conception about the influence of one or another type of food on the course of thyrotoxicosis is not sufficiently grounded. Thus at one time proteins were limited owing to their excitatory action on the secretion of the thyroid gland; objections were raised to substances rich in tryptophan (meat, eggs, milk, cheese, wheat) in which hypothetically the chemical foundation of thyroxin was believed to be; of the fats only cod liver oil was recommended. Such an approach to the diet of the patient with thyrotoxicosis can only be harmful. The decrease in the nutrition of these patients owing to the depletion of fats, carbohydrates and proteins in the organism, on the contrary, demands a diet of full value with an adequate content of all the main foods and vitamins. The opinion about the specific therapeutic significance of some vitamins in thyrotoxicosis is little substantiated and practically not justified. No vitamin, even vitamin C, can lay claim to replacing the enumerated therapeutic remedies even in mild thyrotoxicosis.

In conclusion we want to discuss briefly the importance of some hormonal preparations in treating thyrotoxicosis. These include insulin, estrogens (natural and synthetic) and preparations of the adrenal cortex (cortin, cortisone, etc.). Besides insulin, the use of which in thyrotoxicosis is indicated not only when it is combined with diabetes mellitus (which we have already mentioned), the other

hormonal preparations are effective only when, alongside the thyrotoxicosis, there are symptoms of the insufficiency of the respective endocrinal glands (gonads or the adrenal cortex). It is wrong to prescribe hormonal preparations in thyrotoxicosis without special indications, as some recommend, proceeding from the old conceptions of the antagonism and synergism between endocrinal glands and their hormones.

CHAPTER III

HYPOTHYROIDISM AND MYXOEDEMA

Pathogenesis and Aetiology

The symptom complex known as hypothyroidism and as myxoedema in its more pronounced form arises after experimental total thyroidectomy or in the clinic. It also sets in after inflammatory and purulent processes in the thyroid and after its roentgen radiation, if as a result of these influences degenerative and cicatricial changes develop in the thyroid. The pathological condition thus caused is fully or partly remitted by the administration of a preparation of thyroidin or the thyroid hormone. All this furnishes full grounds for connecting pathogenically the above syndrome with the discontinuation or decreased function of the thyroid and its hormonal production. In addition to the above factors, hypothyroidism and myxoedema may be caused by psychic trauma and various acute (influenza, rheumatism, malaria, etc.) and chronic (tuberculosis, syphilis) infections in their localisation in the organism and outside the thyroid gland. At the same time acute and chronic thyroiditis does not always end in hypothyroidism and myxoedema, and congenital and acquired syphilis of the thyroid, according to data in the literature, causes these conditions very seldom. We have not met a single case among the patients with hypothyroidism and myxoedema we have observed in many years.

Thus, a primary lesion of the thyroid itself is not obligatory for the onset of hypothyroidism and myxoedema. The hypofunction of the thyroid, just as of any organ, may set in secondarily as a result of the derangement of the regulation of its activity by the higher parts of the central nervous system. Definite irritants, such as psychic trauma or an infection, changing the functional correlations of the cortex and subcortical structures, may lead not only to hyperfunction of the thyroid with phenomena of thyrotoxicosis, but also to its hypofunction with changes in the organism of a nature directly opposite to thyrotoxicosis and which are designated as hypothyroidism and myxoedema. It may be assumed that hypothyroidism and myxoedema observed (true more seldom than thyrotoxicosis) during pregnancy, in the climacteric and pubescent periods have a similar primary cerebral genesis. Neurotic conditions which arise in the organism when the genital glands begin or stop functioning (which we have already mentioned), depending on the reactivity of the higher nervous parts, may lead not only to the hyperfunction of the thyroid and thyrotoxicosis, but also to its hypofunction--hypothyroidism and myxoedema.

Supporters of the conception of the narrow synergistic and antagonistic relations between the internal secretion glands seek to explain hypothyroidism and myxoedema during pregnancy, pubescence and the climacteric period by the exhaustion of the thyroid gland owing to its preceding hyperfunction. But their arguments are inconclusive. Clinical observations show that hypothyroidism and myxoedema usually arise in the indicated periods even without being preceded by thyrotoxicosis. The cerebral impulses causing hypothyroidism and myxoedema may be transmitted to the thyroid gland either along the nerve paths bypassing the hypophysis, or through the hypophysis by reducing its thyrotropic activity.

The observations of S. Reichlin are of interest in this respect. He pointed to the dependence of the functional

state of the thyroid on the activity of the nuclei of the hypothalamic region. Excision of three-fourths of the thyroid in normal rats elevated the capacity of its remaining part to absorb radioactive iodine, but this elevated capacity was not noted when the anterior part of the hypothalamus was damaged simultaneously.

In atrophic processes in the hypophysis accompanied by a general decrease of its hormonal activity (Simmond's disease, pituitary dwarfism), more or less pronounced hypothyroid stratification on the main disease is also frequently observed, since in this case the thyrotropic function of the hypophysis usually suffers as well.

Hypothyroidism might arise under the influence of sulfanomides and as a result of prolonged ingestion of iodine. Hidrovitz and Rose observed the development of a myxoedema in a patient who ingested 3-5 mg of iodine daily for 12 years. Rubenstein and Oliner described a case of hypothyroidism in a patient who for six years ingested twice a day 135 mg potassium iodide for bronchial asthma. The authors believe that the high level of iodine in the blood serum and its prolonged surplus supply could lead to a disturbance of metabolic processes in the thyroid and to its primary functional insufficiency. Of course, we also must not rule out the influence of large concentrations of iodine in the blood serum on the thyrotropic activity of the hypophysis with a secondary insufficiency of the thyroid.

For differential diagnosis between primary and secondary, cerebro-hypophyseal origin of hypothyroidism (myxoedema), it is possible to use the thyrotropic hormone which is effective in the latter and does not exert a particular influence in primary functional insufficiency of the thyroid. But thyrostimuline might prove ineffective even in secondary hypothyroidism, if it is of long duration (Binet, Bour, Baulieu).

Clinical Picture

In describing the clinical picture we shall discuss mainly myxoedema. In it all the symptoms, which occur in a somewhat lesser degree in hypothyroidism as well, are pronounced most fully and vividly.

The clinical picture of myxoedema (Fig. 16) is characterised by the prevalence in the organism of a state of inhibition of all the vital functions and it is manifested in decreased function of a number of organs, sluggishness of metabolic processes and a complex of trophic alterations. These processes are generally expressed in physical and mental retardation typical of these patients. The patients are very slow in their movements and actions, talk little and although they reply correctly to questions they think for a long time before answering; they are "slowcoaches". They take little interest in the things around them and are constantly drowsy. At times real psychoses develop, most frequently of a depressive nature.

Fig. 16. Patient, age 24, postnatal myxoedema

Changes in the skin are particularly characteristic of the separate symptoms. The skin of such patients is dry owing to the decreased secretion of the sweat and sebaceous glands, it is pale owing to the insufficient blood supply and pigmentation. This paleness not infrequently is of a yellowish tint because of carotenemia (retardation of the conversion of carotin into vitamin A). As a result of disturbance in innervation the sensitivity of the skin is usu-

ally reduced, but paraesthesia may also be observed. In the skin outgrowths there are acute trophic alterations—the hair is brittle, and falls out on the pubis, axilla and face (of men), at times also on the head; the eyelashes and eyebrows fall out, the nails are brittle with cracks; the teeth crumble and the gums bleed. The skin thickens chiefly owing to oedema and proliferation of the connective tissue. Pillow-like swellings are formed on the back of the feet and hands, in the supraclavicular regions. The swollen legs at times resemble stumps. Frequently oedema is not limited to the skin and also extends to the subcutaneous cellular tissue; then it pits on pressure, which is not the case when the oedema extends only to the skin. The mucosa are also affected by oedema—the lips thicken, the tonsils are enlarged, the voice is husky because of the oedema of the mucosa of the larynx and the vocal chords; the swelling of the mucosa of the tympanic cavity causes deafness.

Some authors explain oedema of the skin in myxoedema solely by the storing in it of mucin which possesses a semiliquid consistency, viscidity and extensibility. But this is not confirmed by all the authors and does not always explain the frequently encountered simultaneous oedema of the subcutaneous cellular tissue. We hold that a different origin of oedema in myxoedema is more probable. With the hypofunction of the thyroid and insufficient concentration of thyroxin in the organism the oxidation processes in the cells and tissues are reduced; a surplus quantity of insufficiently oxidised intermediate products of metabolism accumulate in them, with a shift of the active reaction towards acidosis and a resultant elevation of hydrophilia.

The state of the cardiovascular system in myxoedema is also typical. The pulse rate is decreased (up to 40 beats per minute), it is feeble and arterial pressure is low; the heart is enlarged and the heart sounds are distant. Roentgenological studies show that the diameter of the heart

is increased and reaches up to 20-22 cm (instead of 12-15 cm); the diameter of the aorta is also enlarged, the heart pulsation is feeble and superficial. The electrocardiogram shows low voltage of the waves with a flattening of the P and T waves and a decrease in the amplitude of the complex QRS; not infrequently there is a block of the right branch of the bundle of His and a lengthening of the P-Q interval. The lesion of the myocardium and its enlargement, the so-called tonogenic dilatation, are connected mainly with the neurogenic drop of the cardiovascular tones and possibly also with the imbibition of the myocardium with the oedematous fluid.

In the red blood, there is most frequently hypochromic anaemia, more seldom hyperchromic anaemia and still more seldom, haemolytic anaemia. The pathogenic connection of anaemia with myxoedema is confirmed by its combination with other hypothyroid symptoms. Anaemia accompanying myxoedema responds harder to medication with thyroid preparations than other symptoms of hypothyroidism. To treat anaemia successfully in myxoedema it is necessary, besides thyroid preparations, to use antianaemic agents. The onset of anaemia in hypothyroidism is evidently of an intricate origin and depends not only on the functional insufficiency of the thyroid (Olmer, Erlande, Abignon). Buso, Olavarrieta, and Suarez, who studied in 11 patients with hypothyroidism the life span of erythrocytes marked *in vitro* by Cr^{51} and introduced back into the organism, arrived at the conclusion that anaemia in hypothyroidism is possibly connected with the shortened "life" of the erythrocytes. In the leucocytic picture there are often lymphocytosis, at times monocytosis and eosinophilia. The volume of circulating blood is decreased and blood coagulation is elevated.

In contrast to patients with thyrotoxicosis who, together with great appetite, have diarrhea or spastic constipation, patients with myxoedema have a low appetite and paretic constipation. At times the patients have no bowel move-

ment for several days. The abdomen is flatulently distended; owing to the fact that the intestines are filled with gas the sound over the entire abdomen is tympanic or with a tympanic tone, it is impossible to palpate various parts of the large intestine. Symptomatic treatment in such cases does not produce any particular effect.

The course of vital processes in myxoedema is marked by inhibition and determines the low level of metabolism in these patients. This is true of all kinds of metabolism, but against the background of their general inhibition, processes of assimilation prevail over processes of dissimilation. Protein metabolism is characterised by a low positive nitrogen balance, even if the content of protein in the food is low, but proteolysis and the formation of urea from the deaminated proteins proceeds normally; the level of keratine excreted in the urine is lower than usual.

The content of uric acid is reduced both in the urine and in the blood, probably caused by the decreased activity of the intestinal glands which are of great importance in the formation of uric acid (A. V. Palladin, H. Zondek).

Derangement of the carbohydrate metabolism is expressed in an elevated carbohydrate tolerance and the intensive storing of carbohydrates in the liver; the sugar level in the blood remains within the lower boundary of the norm; even with a considerable sugar load there is a low sugar curve and no glucosuria is observed. At times it cannot be induced even by a dose of adrenalin double the one usually employed. All this depends on the deficiency of thyroxin in the organism, which acts on the carbohydrate exchange in the same direction as adrenalin.

Derangement of lipid metabolism in myxoedema leads to obesity. This is explained, on the one hand, by the lower influx of fat from the periphery to the liver (owing to the surplus storage of glycogen in it) and its burning up, and, on the other, by the elevated lipophilia of the tissues owing to hydrophilia.

The cholesterol level in the blood in such patients is subject to big fluctuations; the cholesterol content is frequently raised substantially and may reach up to 600 mg per cent.

In myxoedema, in contrast to thyrotoxicosis, evidently a part is played by the smaller excretion of cholesterol in the bile, the content of which in the bile is reduced.

As a result of elevated hydrophilia of the tissues the water balance of patients with myxoedema is positive. They have oliguria with a higher concentration of urine; the sodium chloride exchange is not disturbed, the content of chlorides in the blood is normal and a load with sodium chloride correspondingly increases its excretion.

In myxoedema, as can be expected, the content of iodine—protein-bound and non-protein—both in the thyroid and in the blood, is either below norm or at the lower boundary of the norm. The iodine-protein fraction in the blood comprises approximately 2 per cent (the norm is 8 per cent and in thyrotoxicosis, 25 per cent). The uptake of radioactive iodine by the thyroid drops sharply. According to data of the All-Union Institute of Experimental Endocrinology (Y. A. Kolli and N. A. Shtegeman), it comprises in myxoedema 1.4-3 per cent two hours after the ingestion of I^{131}; 24 hours later there is a total absence of I^{131} absorption. For the milder forms of hypothyroidism the uptake is 4 per cent after two hours and 6.9 per cent after 24 hours (as against 8.5 and 21.3 per cent normally).

Ascertainment of the functional capacity of the thyroid with the aid of radioactive iodine may help in differential diagnosis between a neurotic condition when bradycardia, low arterial pressure, puffiness of the face and more seldom of the extremities, particularly in the morning, are of a purely neurogenic character, and myxoedema, in which all these symptoms are indications of the hypofunction of the thyroid. It is exceedingly important to establish this when assessing the general condition of the patient and deciding on the necessary medication.

Retardation of all the vital functions and the low level of all kinds of metabolism in myxoedema are expressed in an exceedingly low consumption of oxygen by these patients even in a state of rest. H. Zondek rightly stresses that the low consumption of oxygen by these patients depends not on sluggishness and their limited movement, but on the decreased oxidation processes in their tissues and cells. Their basal metabolism is always below norm (below —10 per cent or at the lower boundary of the norm: —10 per cent to —5 per cent). The non-conformity between the basal metabolism values and the severity of disease, mentioned earlier when discussing thyrotoxicosis, is even more strikingly pronounced in myxoedema, particularly in very severe forms when the basal metabolism may be not lower than —20 per cent. A level of the basal metabolism below —40 per cent is observed infrequently and much more seldom than high values of the basal metabolism in thyrotoxicosis. The reduced basal metabolism might be caused, besides the functional state of the thyroid, by cardiac insufficiency, anaemia, nephroses, insufficient or protein-low diet, obesity (in which the values of the basal metabolism depend also on the method of calculation—account of the weight in kilograms), some endocrinal diseases (decompensated diabetes mellitus, Addison's disease, hypogenitalism, etc.). All this must be remembered so as not to attach decisive significance to the values of the basal metabolism when they diverge with the clinical picture.

Houston draws attention to the diagnostic value of the Woltman symptom in myxoedema; it consists in a considerable retardation of the relaxation phase after the normal period of the contraction phase when inducing the Achilles tendon reflex. With the aid of the "myxoedema reflex" he succeeded in diagnosing in five patients an indistinctly pronounced form of hypothyroidism. After the ingestion of thyroidin the pathological phenomena disappeared.

The thyroid in adult myxoedema, in view of its prolonged hypofunction, is either hypotrophic or atrophic. It is not palpable but, of course, the decrease of its size cannot be judged by palpatory data alone, since even a normal thyroid can seldom be palpated. That is why this symptom by itself does not provide grounds for diagnosing myxoedema in doubtful cases. In histological studies of the thyroid in myxoedema proliferation of the connective tissue and degenerative changes of the parenchymatous tissue are found. Abundant proliferation of the connective tissue makes the thyroid at times palpable and it feels dense to the touch. Consequently, a palpable thyroid does not exclude myxoedema.

In secondary myxoedema, according to data of Bastenie (22 autopsies over 25 years), degenerative changes in thyroid tissue recede to the background, while first place is held by colloidal involution as an indication of the secretory insufficiency of the thyroid. Simultaneously noticeable changes in the hypophysis are found. In general the histological picture of the thyroid is the same as in experiments after the excision of the hypophysis.

Retardation of metabolic processes, characteristic of myxoedema, is especially strikingly pronounced in children during the period of growth and development of the organism. In addition to the above-enumerated symptoms of myxoedema seen in adults, in children retardation of physical, sexual and mental development come to the foreground. The cause of myxoedema in children is mainly congenital hypo- or aplasia of the thyroid and its functional insufficiency as a result of anomaly of prenatal development (congenital defect) or prenatal infection (syphilis, etc.). Clinically, myxoedema becomes pronounced in a child either immediately after birth or immediately after weaning, when the infant's organism does not get any more of the thyroid hormone contained in mother's milk; or myxoedema develops at a later period when the thyroid gland, dynamically insufficient from birth, becomes ex-

hausted prematurely, and its insufficiency begins to manifest itself. Moreover, in any period of a child's life myxoedema might develop in connection with the infections which affect the thyroid in children the same way as in adults.

The earlier the age at which myxoedema arises, the more sharply pronounced are the symptoms of the physical, sexual and mental underdevelopment of the child. In congenital myxoedema children develop poorly, they do not begin to walk for a long time, teething and the closing of the bregmatic fontanel is delayed for a long time, the appearance of ossification centres and the closing of the epiphysial lines are delayed considerably. Owing to the disturbance of normal growth of the cranial bones, such children have a relatively large skull and a sunken bridge of the nose. The long bones are short and broad but the general proportions of the body are preserved; the face is puffy, the mouth cannot hold the thickened tongue and it protrudes; they have a husky voice, a big belly and frequently umbilical hernia. Such children can hardly keep their head up, they have a senseless stare, often do not recognise their parents and do not turn when called. Their physical development is very slow—five-year-old children resemble one-year-olds, ten-year-, three-year-olds and adults look like children (Fig. 17, 18). The sexual glands, the internal and external genital organs of children with myxoedema, sharply lag in development all the time. Secondary sexual features (mammary glands, the growth of hair) do not appear. Mental backwardness in children does not pass with age and at times reaches idiocy. In acquired myxoedema the physical, sexual and mental development of the child usually is arrested at the age at which the disease set in.

It is important to differentiate in time myxoedema in children from other diseases characterised by one or another form of retardation in the development of the organism. This is first of all pituitary dwarfism. In this

Fig. 17 Patient, age 6, with inborn myxoedema Height 83 cm (corresponds to 3 years)

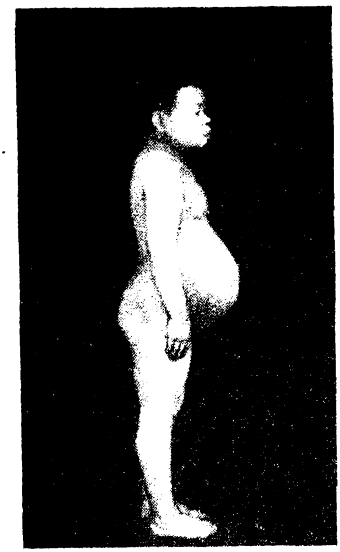

Fig 18 Patient, age 29, with inborn myxoedema Height 119 cm (corresponds to 7½ years)

disease there is also the sharply pronounced physical and sexual underdevelopment of children with normal proportions of the body, if, moreover, there are also hypothyroid stratifications (which we mentioned earlier) the patients outwardly, too, resemble patients with myxoedema. But as distinct from the latter, their intellect is fully preserved and they are capable of doing mental work.

It is more difficult to confuse myxoedema with chondrodystrophy, in which the dwarfish growth of the patients does not affect their sexual and mental development, while the derangement of the proportions of the body (long body, short extremities, particularly their proximal

sections, huge skull with eminent frontal and parietal protuberances) are so typical that the disease is easily diagnosed by them alone. The same may also be said with regard to rickets, in which the patients, besides short stature, moreover disproportional, have no other symptoms inherent in myxoedema. The Langdon-Down disease, congenital malformation, is at times mistaken for myxoedema. In such patients with acute mental backwardness there is also a certain lag in growth (less pronounced than in myxoedema) and at times also in sexual development. The outward appearance of the patients and their behaviour are of great help in differential diagnosis. People who suffer from the Langdon-Down disease have a small skull, low forehead, slanting narrow palpebral fissures, there is no puffiness of the face and skin oedema. They are restless, fussy, at times have a palpable enlarged thyroid with clinical symptoms of its hyperfunction.

As for endemic cretinism, it is very similar to congenital myxoedema which in this case, too, is determined by insufficient production of the thyroid hormone. But in endemic cretinism the decreased function of the thyroid depends most frequently not on the hypo- or aplasia of the thyroid but on the destructive fibrocystic alterations developing in it with destruction of the parenchymatous tissue. As distinct from myxoedema, which is also called sporadic cretinism, endemic cretinism is encountered only in endemic goitre areas and the thyroid is usually noticeably enlarged; its size, form and consistency differ (see Chapter 5).

Treatment

Treatment of hypothyroidism and myxoedema both in children and adults consists in giving the organism the thyroid hormone it lacks. Attempts have been made to transplant into the organism of the patient thyroid tissue for therapeutic purposes. The thyroid of animals and man

was used. The thyroid was transplanted in various parts of the body but the effect was brief; the transplanted thyroid did not grow into the organism and gradually dissolved, the influx of the active hormonal element from it into the organism ceased, and the pathological symptoms recurred. According to the observations of some authors, the best result is obtained by homotransplantation of the thyroid on a vascular pedicle (N. A. Bogoraz, V. L. Khenkin, T. Y. Gnilorybov) with strict observance of the blood group.

Transplantation may at times lead to temporary thyrotoxicosis since the saturation of the patient's organism with thyroxin from the transplanted thyroid may be excessive at a definite stage. Transplantation of a pathologic thyroid taken from thyrotoxic patients to patients with myxoedema, recommended by some authors (V. A. Oppel, and others), is absolutely unjustified.

The efficacy of one or another method of transplanting the thyroid, a question still being debated, has lost its poignancy because treatment of myxoedema and hypothyroidism with thyroidin administered perorally has fully justified itself and is widely used at present. This preparation consists of a powder or tablet of desiccated thyroid of animals. Its efficacy is exceedingly high. Under its influence pathogenic symptoms are mollified swiftly, at times in a few days, and then disappear altogether. Systematic timely ingestion of thyroidin enables adult patients not to feel their disease and to preserve their working capacity; it normalises the physical, sexual and mental development of children. But this is replacement therapy. Should the patient omit treatment, even if only temporarily, all symptoms recur with the same force.

The dosage of the preparation depends on the degree and severity of the disease. Adults are usually given 0.1-0.2 g of thyroidin, 2-3 times a day; when the symptoms are mollified the dose is gradually reduced to 0.1g, 1-2 times daily, until a full effect is obtained. At times to main-

tain the results achieved it is sufficient to ingest 0.1 g of thyroidin every other day; if the condition of the patient grows worse the dose is again increased. In case of large doses it is advisable to interrupt treatment for a day every 2-3 days.

The pulse, weight and blood pressure of patients treated with thyroidin should be checked to avoid overdosing. Acceleration of the pulse rate, drop in weight and an increase of blood pressure are an indication for temporary discontinuation of treatment or for a reduction of the dose.

At first we were apprehensive of prescribing thyroidin for patients with a combination of hypothyroidism and hypertension, the more so, sclerosis of the aorta or coronary sclerosis. We thought that elevation of the vascular tonus in the periphery with the aid of thyroidin might be an additional load on the heart, the tonus of which is already low owing to hypothyroidism, and that this might accelerate the onset of cardiac insufficiency. But having no other means of treating hypothyroidism in such patients, we were compelled to use this preparation. We began treatment cautiously, using at first small doses and gradually increasing them in case of necessity. It turned out that under the influence of thyroidin the work of the heart, far from growing worse, even improved. Phenomena of coronary or myocardial insufficiency, noticed at times before treatment, disappeared. Stenocardia attacks, of which V. G. Baranov writes, were not observed by us. The favourable effect of thyroidin in a combination of hypothyroidism with hypertension is determined, it may be assumed, not only by the reduced concentration of cholesterol in the blood, which can only retard progressing atherosclerosis, but also by the elevation, under its influence, of oxygen consumption by the myocardium which suffers particularly in case of coronary atherosclerosis from hypoxia inherent in hypothyroidism.

In severe myxoedema, congenital or acquired at an early

age, children may be given thyroidin 0.1-0.3 g daily, with a reduction of the dose and the subsequent establishment of a maintenance dose, according to the principle indicated above for adults. For small children with not very severe forms of hypothyroidism some authors suggest as a guide for determining the dose of thyroidin the height of the patient in a sitting posture. For a height from 30-35 to 100 cm the dose is from 0.01 to 0.1 g daily.

Of late some authors (Spanár, Baláž) have started to use triiodothyronine, approximately 10 times more effective than thyroidin, for the treatment of myxoedema. According to data of these authors, 40-100 gamma of the preparation, already on the 5th-15th day considerably mollify myxoedema symptoms (the pulse rate is increased, the cholesterol level in the blood is reduced, oedema and dryness of the skin is lowered and the bowel movement is normalised). But just as in treating with thyroidin, omission of therapy rapidly leads to disappearance of the effect obtained.

Triiodothyronine is particularly indicated in severe hypothyroid conditions where urgent aid is needed, for example, in a myxoedematous coma, described in literature (we have not seen such cases) which might end lethally. Such a coma strikes patients with severe myxoedema who have not received replacement therapy for a long time. The most characteristic symptom of this condition is a sharp drop of body temperature. To bring the patient out of the comatose state it is advisable, in addition to triiodothyronine, to warm the body and to use adrenal cortex preparations.

Dysthyroidism

V. D. Shervinsky, one of the founders of Soviet clinical endocrinology, uses the term dysthyroidism to designate a condition when the clinical manifestations do not give a clearly pronounced picture of thyrotoxicosis or myxo-

edema and there are only separate symptoms inherent in a hyper- or hypofunction of the thyroid. Correspondingly, he divides dysthyroidism into Bazedowic and myxoedematous. To explain the pathogenesis of dysthyroidism Shervinsky assumes "the plurality of the composition of the thyroid incretion". According to his idea, dysthyroidism arises when derangement of the thyroid function affects not the incretion as a whole, but only its separate ingredients and the clinical picture reveals not the entire hyper- or hypothyroid symptom complex but only separate symptoms, which correspond to the changes in the composition of the incretion. Shervinsky was aware that his conception of dysthyroidism was shaky and he aptly described it in the following words: "We may say this, but we cannot prove it." We mention this conception only because at the time it had many supporters among Russian and foreign endocrinologists. There are undoubtedly forme fruste of endocrinal diseases, including thyrogenic, with one or two symptoms, which we mentioned earlier; they depend, however, not on the complexity of the composition of one or another hormone and the differentiated action of its separate component parts on the organism, but on the different reaction of various organs and systems to the single pathologic element.

Other authors use the term "dysthyroidism" to designate syndromes which consist simultaneously of symptoms inherent in thyrotoxicosis and hypothyroidism (myxoedema). The patient with an enlarged thyroid, for example, has a combination of tachycardia and loss of weight with dryness of skin, chilliness and drowsiness or a combination of hyperhidrosis, diarrhea and exophthalmos with bradycardia, low arterial pressure and general inhibition. Such syndromes are really encountered. From the standpoint of the clinicist they can be called dysthyroidism, indicating thereby that the clinical manifestations make it possible to judge only the disturbance of the thyroid function, but not the nature and direction of this derangement.

But this does not mean that two opposite conditions —hypofunction and hyperfunction—exist simultaneously in the activity of the thyroid. In syndromes with symptoms of hyper- and hypofunction, the thyroid activity is affected only in one direction, but to this altered function different organs and systems, depending on the state of their neuroceptors, might react in an opposite way.

The impossibility of gaining from the clinical picture of dysthyroidism a correct idea of the nature of the thyroid functional disorder makes it hard to choose the suitable methods of therapy. The clinicist has to resort with caution now to thyroidin, now to microdoses of iodine or other preparations inhibiting the function of the thyroid and watch how the pathological manifestations change under their action. Not infrequently the clinicist has to refrain from special treatment designed to normalise the function of the thyroid because the mollification of some symptoms under its influence may be accompanied by an exacerbation of other, opposite symptoms.

The use of radioiodine diagnosis for determining the functional state of the thyroid helps to some extent to direct treatment of dysthyroidism along the proper channel.

CHAPTER IV

THYROIDITIS (STRUMITIS)

Pathogenesis and Aetiology

Inflammatory processes can arise in the thyroid, just as in any organ of the human body. These inflammatory processes are of an exudative, fibrotic, purulent and gangrenous nature; the latter two develop into an abscess and gangrene of the thyroid. Inflammation of the thyroid is called thyroiditis, and that of a thyroid gland affected with goitre, strumitis. In all other respects there is no difference between thyroiditis and strumitis and everything that will be said about the first applies to the second as well. Any acute or chronic infection with different primary localisation can be the aetiological factor of thyroiditis. Thyroiditis is seen in streptococcal, bacillary, parasitary, virus and other infections, but most often in influenza and angina. Infectious matter gets into the thyroid with the blood, lymph, or through contact with adjacent organs affected by the infectious process. At times the inflammatory process is localised in the thyroid without affecting other organs.

Thyroiditis can also arise under the influence of intoxications. Thyroiditis in lead and carbon monoxide poisoning has been described (Schultze). V. V. Khvorov and Scheithauer hold that thyroiditis can be caused by the toxic action on the thyroid of large quantities of iodine introduced in the organism for a long time. It is difficult

to agree with this view. First, it is a fact that the iodine absorbed by the thyroid is used for the formation of the thyroid hormone which partly goes for the current needs of the organism and partly is stored in the follicular colloid. The unutilised iodine is excreted in the urine. The excessive introduction of iodine into the organism leads mainly to greater storing of the hormone in the colloid and more intensive excretion of iodine in the urine and not to a higher concentration of iodine in the follicular cells. Secondly, iodine is a physiological inclusion in the follicular cells of the thyroid and some or other fluctuations in its content could hardly have a toxic effect on these cells.

The supposition voiced by V. V. Khvorov that Jod-Basedow resulting from the ingestion of large doses of iodine begins with thyroiditis, is also highly improbable. The author does not present any proof. It should be assumed that the ways of development of Jod-Basedow are different. The influx of excessive quantities of iodine into the organism leads to greater iodine exchange and to an activation of the thyroid function closely connected with iodine metabolism.

Hyperaemia and exudation, proliferation and desquamation of the epithelium and proliferation of the connective tissue elements are observed in sections of the thyroid which suffered from the inflammatory process in thyroiditis.

Clinical Picture

Thyroiditis is characterised by a rapid enlargement and painfulness of the thyroid; patients complain of pain and a feeling of stress in the thyroid region (in thyrotoxicosis the enlarged thyroid is painless). If the inflammatory focus is near the soft tissues covering the thyroid there is also rubeosis of the thyroid region which feels hot to the touch. The temperature of the body rises, at times considerably, and in purulent inflammation of the thyroid it is

of a hectic nature. On the part of the blood there is leucocytosis, a leucocyte shift to the left and accelerated E.S.R. There are also other symptoms inherent in any infection—weakness, a feeling of exhaustion, headaches, insomnia, etc. In tubercular and syphilitic thyroiditis there are also general symptoms characteristic of each of these diseases. Complications of thyroiditis include difficulty in swallowing, respiration and speech, pain in the occiput and behind the ears, puffiness of the face and dilatation of the corresponding veins. This is explained by the pressure of the inflamed thyroid on the adjacent organs, nerve trunks and vessels and also by the oedema of the mucosa of the larynx and vocal cords.

Thyroiditis may be acute and end in a few days, or subacute and continue for weeks, or chronic and drag out for months. Correspondingly, the pronouncement of the symptoms is changed. Chronic thyroiditis may have remissions and exacerbations of various duration. Moldover holds that such a course is characteristic of subacute relapsing thyroiditis. One or another course of the disease depends not only on the nature of the infection which caused it, but also on the reactivity of the thyroid and the organism as a whole.

The outcome of thyroiditis differs. The inflammatory process may pass without trace or end in cirrhosis of the thyroid with its puckering and decrease of its function. An abscess on the thyroid might open through the skin and then the process ends in self-cure, or it might burst into the lungs or mediastinum with a subsequent development of a corresponding clinical picture of an abscess of the lungs or mediastinum. But at times (true, seldom) the thyroid, enlarged owing to thyroiditis, does not decrease in size, notwithstanding the disappearance of the local and general symptoms of inflammation, and the thyroiditis is replaced by thyrotoxicosis or hypothyroidism; the latter might develop even when the consistency of the thyroid offers no grounds for supposing cirrhotic alterations. The

development of thyrotoxicosis and hypothyroidism during the period of thyroiditis itself is observed more seldom since the inflammatory process by itself can both activate or inhibit the function of the thyroid. Volpe, Johnston and Huber believe that in very severe thyroiditis thyrotoxicosis might arise in consequence of necrosis of the thyroid and the influx of a large quantity of the thyroid hormone into the organism. Thyrotoxicosis is then replaced by a hypothyroid state with a low concentration of the hormone in the blood.

Thyrotoxicosis and hypothyroidism can be recognised against the background of thyroiditis by the special symptoms inherent in each of these conditions, if they are more or less pronounced. In cases of a combination of thyroiditis with thyrotoxicosis, even not sharply pronounced, the attention of the physician is often shifted to the latter as the more frequently encountered, while the first is overlooked since its symptoms are ignored. This is also the case at times in thyroiditis without thyrotoxic phenomena. A diagnosis of thyrotoxicosis is made solely on the basis of the enlarged thyroid, without regard for the other symptoms, the treatment is concentrated upon it and the thyroiditis is left without medication. We have come upon this in our work and have directed the attention of doctors to it. On the other hand, inflammatory and purulent processes in the larynx are at times mistaken for thyroiditis. That is why doubtful cases always require consultation with a surgeon and otolaryngologist.

The so-called Riedel's struma and Hashimoto's struma represent a special type of chronic thyroiditis. As distinct from the above-mentioned chronic thyroiditis in which the connective tissue is drawn into the process secondarily, after the parenchymatous tissue, Riedel's struma begins with the proliferation and the subsequent cirrhosis of the connective tissue which only secondarily leads to the destruction of the parenchymatous elements. Shrunk follicles are found only on the periphery of the affected parts

of the thyroid. Indistinctly pronounced lymphoid infiltration at the beginning of the disease is also observed. Most frequently, separate parts of a lobe of the thyroid are affected, but the process can also spread diffusely to the entire gland. Fibrous changes might extend beyond the bounds of the thyroid to adjacent organs with the formation of fibrous cohesions between them and the thyroid. As for the skin over the thyroid, it remains loose and can easily be folded.

Clinically, Riedel's struma is characterised by exceptional density of the affected sections when palpating the thyroid. That is why it is named "iron-like" or "wooden" struma. Such a struma is immobile and painless during palpation. The growth of the struma, just as the proliferation of the fibrous cohesions embracing it and the adjacent organs, often leads to pressure on the trachea, oesophagus and other contiguous organs, with corresponding compression phenomena (difficulty in breathing and swallowing, husky voice, etc.).

In contrast to Riedel's struma which is observed at the age of up to 40 with equal frequency both among men and women, Hashimoto's struma is encountered primarily among women after 40-50 years of age. Abundant diffused infiltration of lymphoid tissue is observed in the thyroid with subsequent destruction of the parenchymatous elements and proliferation of the connective tissue. The process is concentrated in the thyroid itself and no cohesions with the adjacent organs are formed.

The thyroid in Hashimoto's struma is also exceedingly dense but less than in Riedel's struma. It usually has an even surface and more seldom a nodular surface. The thyroid is painless and hardly moves during palpation. Compression phenomena on contiguous organs are less frequent in Hashimoto's struma than in Riedel's struma, since here they are determined by the pressure of the enlarged mass of the thyroid and not by the cohesion process. But hypothyroidism is a frequent complication of

such a struma. Morgans and Trotter consider the decreased ability of the thyroid to bind iodine with organic compounds as characteristic of Hashimoto's struma. The administration of perchlorate therefore facilitates the swifter excretion of iodine from the thyroid.

Not all the authors regard Hashimoto's struma and Riedel's struma as two distinct forms of chronic thyroiditis. There is a view that these two forms of disease of the thyroid are two consequent stages of the one and the same chronic process (V. A. Akimov, L. P. Elmanovich and others).

The exceedingly great density of the thyroid, particularly of its separate sections in Riedel's struma, its complete immobility (in Riedel's struma) and partial immobility (in Hashimoto's struma), the absence of thyrotoxic symptoms naturally make the doctor suspicious of a malignant tumour. The absence of enlarged regional lymph nodes, skin cohesions and cachectic state of the patient, which is seen in malignant tumours of the thyroid, is of aid in differential diagnosis. At times, however, the diagnosis becomes clear only in the histological study of the thyroid tissue. The aetiology of Riedel's struma and Hashimoto's struma has not been ascertained so far.

Treatment

Treatment of thyroiditis (strumitis) must be the same as of any other inflammatory process, with account of the infection that caused the thyroiditis. Local antiphlogistic remedies, just as antibiotics, should be used from the very beginning. The use of cortison and adrenocorticotropic hormone has yielded positive results.

The possibility of sharp compressional complications developing into an abscess makes it obligatory for a surgeon to participate in observing the patient. Special measures to influence the function of the thyroid are recommended only when symptoms of thyrotoxicosis or

hypothyroidism become evident after the inflammatory process is remitted. Treatment of these conditions, discovered in the period of thyroiditis, before removing the inflammatory process which maintains it, is useless; it can only divert the attention of the doctor from combating the main disease. Resection of the affected part of the thyroid with the excision of the cohesions surrounding the adjacent organs is indicated in Riedel's struma. Postoperative relapses are possible. Surgical treatment is also preferable in Hashimoto's struma when there are compressional phenomena. Postoperative relapses are less frequent than after operations for Riedel's struma.

Some authors advise roentgenotherapy in Hashimoto's struma, pointing to the special sensitivity of the thyroid to roentgen rays in this form of chronic thyroiditis. V. R. Klyachko describes a 52-year-old patient in whose case Hashimoto's struma and the accompanying hypothyroidism (also confirmed by radioiodine diagnosis) disappeared after the ingestion of thyroidin for four years. An examination of the patient a year after the omission of thyroidin revealed no change for the worse in her condition.

CHAPTER V

ENDEMIC GOITRE

Definition

Endemic goitre is the name of a disease of the organism which is accompanied by an enlargement of the thyroid and is found only in definite geographical boundaries or so-called biogeochemical provinces characterised by iodine deficiency in nature.

This disease affects more or less considerable masses of the population and has its own laws of development, which set it apart from other diseases accompanied by thyroid enlargement of an infectious nature, from a primary thyrotoxic diffuse goitre or Basedow's disease and from malignant neoplasms. Its connection with the specific conditions of the environment has been firmly established and this is the principal and essential characteristic of endemic goitre as a disease.

The term "endemic goitre" is generally recognised. It is officially accepted by the World Health Organisation, which publishes a special bulletin on this problem, and by scientific and applied medical institutions of the Soviet Union. At times endemic goitre and especially euthyroid goitre are called simple, local goitre. Some authors who insufficiently differentiate diseases of the organism, which vary for their aetiology and pathogenesis and are accompanied by goitre as a local symptom, try to preserve the old term, "goitre disease". Such a unification is utterly groundless. The term "goitre" signifies merely a symptom, i.e., a local change of the configuration of the neck,

most often in view of the enlargement of the thyroid, which frequently reaches a substantial size. But the term "goitre" should not be abused. Only on the basis of a careful examination in each separate case can the presence of the disease be established. But one must not go to the other extreme and ignore small thyroid enlargements seen among the population in some region.

For a clinical study of a patient with goitre it is important not only to note an enlargement of the thyroid, but also to be certain of the pathologic importance of this enlargement. The anatomo-physiological distinctions of a normal organism of man, examined in the ecological aspect, must have some differences in various geographical areas. This particularly applies to the condition of the thyroid. That is why Eggenberger's assertion that half of all mankind is a carrier of goitre is not convincing. Areas of high endemicity are at the same time areas of endemic cretinism. In cretins the thyroid undergoes the greatest changes, which also take place to one or another extent in each patient with endemic goitre.

When the thyroid is enlarged the existence of nodules in the thyroid tissue, i.e., the formation of a nodular endemic goitre, offers indisputable evidence of the organism's disease. A diffuse enlargement of the thyroid alone by far not always attests to the existence of the disease. In particular, it might constitute the physiological adaptation of the organism to the environment and might represent a compensatory reaction of the organism to the specific features of the environment characteristic of a goitrogenous region. This compensatory reaction of the organism which adapts itself to the special conditions of the environment might take place without an enlargement of the thyroid even in an area of high endemicity and cretinism. In each goitrogenous region the goitre has its morphological and clinical distinctions, but there are no grounds for contrasting the endemic goitre of various geographical areas. The so-called goitre epidemics might

represent not only the frequently observed rise in the incidence of endemic goitre but also mass infectious toxic thyroiditis, which is in a class by itself. In places free of endemic goitre so-called sporadic, frequently familial, goitre is encountered. At times, however, it turns out that cases of sporadic goitre reflect the existence of indistinctly pronounced phenomena characteristic of a district unfavourable as regards goitre. A deeper study of the incidence of goitre in these localities may reveal a widespread, true, small thyroid enlargement, especially among children of school age, while goitre among adults is actually found more frequently than it seemed at first glance. In these cases it is necessary to speak not of goitrogenous regions, but of districts of endemic thyroid enlargement. Endemic goitre is also found among various species of animals. The above gives an idea of the biological and the social significance of the endemic goitre problem.

History

Endemic goitre was known to doctors of antiquity—in India, China, and Greece. Much later, in 1275, Marco Polo mentioned goitre in Ferghana Valley. In the 16th century, Paracelsus spoke of the connection between goitre and cretinism in Switzerland. In 1736, information was published about the existence of goitre in the Lena River valley in Russia.

Russian investigators (M. F. Kandartsky, N. Lezhnev, V. S. Levit, I. A. Aslanishvili, S. M. Masumov and many others) rightly assessed the great significance of the endemic goitre problem. The most important and thoroughgoing studies of many aspects of this problem have been made in the last 30 years. Great successes in combating this disease have been scored in the Soviet Union thanks to the participation of scientists of different specialities in the study and campaign against goitre and the organisation of a special network of antigoitre institutions. The

All-Union Institute of Experimental Endocrinology has taken a leading place in the methodological guidance of the study of endemic goitre and the campaign against it. The U.S.S.R. conferences sponsored by the Institute jointly with the Central Goitre Commission have helped to exchange experience and plan anti-goitre activities. In recent years research work in this field designed to solve special questions of the pathogenesis of goitre has been conducted in the aspect of the unity of the organism and its environment, the role of trace elements in the physiology of animal organisms and the use of radioactive elements. The study of endemic goitre in definite geographical boundaries or in biogeochemical provinces (after A. P. Vinogradov) demands a number of comprehensive investigations. Among them is the special examination of the thyroid of the entire population; determination of the weight of the thyroid according to autopsy data; investigation of the sanitary-hygienic living conditions of the population and its diet; a study of the clinical manifestations of goitre and its morphology. A study of the environment is made with a geochemical characterisation of the locality, including measurements of the iodine content in nature, characterisation of the water and the iodine content in the soil and water, in the food products of plant and animal origin.

Methodological guidance of the constant anti-goitre campaign in the localities is given by the special anti-goitre committees in the public health ministries of the republics and in the regional public health agencies. The struggle against this disease has been made a task of state importance in the Soviet Union. At present in some regions which in the past were notorious as areas with a large incidence of goitre and cretinism, this disease has been completely stamped out. Soviet experience in combating endemic goitre is successfully utilised in a number of People's Democracies. Extensive work in combating endemic goitre is also conducted in other countries.

Distribution of Endemic Goitre in the World and in the U.S.S.R.

A uniform method of determining the condition of the thyroid is very important in the study of the distribution of endemic goitre. A modified Swiss classification of five degrees of thyroid enlargement has been accepted in the U.S.S.R. Let us note that lately the World Health Organisation has been making a somewhat simplified classification which, however, can easily be compared with the one adopted in the Soviet Union. Thus the I and II degrees in our country correspond to the invisible but palpable enlargement of the thyroid which, according to the present-day international classification given in the latest issue of the bulletin of the World Health Organisation, is listed in the first group of invisible but palpable goitre. Zero according to our classification and the zero group according to the new classification designate a normal thyroid, i.e., an absence of its enlargement. The second group, visible goitre, according to the international classification, corresponds to our III and IV degrees of thyroid enlargement, i.e., such an enlargement which in our country too is already called a goitre. The third group, large goitre, conforms to our V degree of thyroid enlargement which we describe as a huge goitre.

Therefore, in studying the materials of the distribution of goitre in the world or comparing the degree of severity of goitre endemy in different parts of the world, it is necessary to take into account the percentages by degrees of thyroid enlargement or goitre groups. At the same time it is also necessary to ascertain the form of goitre, i.e., diffuse, nodular or mixed, and also the functional changes. The following degrees of severity of endemic goitre are differentiated: mild, moderately severe and severe. The severity of goitre endemy can also be judged to a certain extent by the ratio which characterises the proportion of goitre incidence (III-V degrees of

Fig. 19. Endemic diffuse goitre, III degree.

Fig. 20. Endemic diffuse goitre, IV degree.

thyroid enlargement) among adult men and women. The closer this ratio is to one, the more severe the goitre endemy.

Here is the classification adopted in the U.S.S.R.: Zero—the thyroid is not palpable or at times is little palpable; I degree of thyroid enlargement—the enlarged thyroid is clearly palpable but in swallowing the enlargement is not noticeable to the eye; II degree—the enlarged thyroid is well palpable and its enlargement is noticeable when the patient swallows; III degree (Fig. 19)—"thick neck", the enlarged gland is well seen; IV degree (Fig. 20)—sharply enlarged gland, distinctly pronounced goitre which changes the configuration of the neck; V degree (Fig. 21-22)—the goitre is very large. Account should be taken of the fact that in the period of sexual maturing and in case of women in the period of menstrual cycles and pregnancy the thyroid often increases to the II degree and at times to the III degree with a slight elevation of its function, even when daily influx of iodine into the organism is

Fig. 21. Endemic diffuse goitre, V degree.

Fig. 22. Endemic diffuse goitre, V degree.

adequate. It is obvious that such physiological enlargement of the thyroid, seen very frequently in children of school age, must not be regarded as a disease of endemic goitre, but during examinations these thyroid enlargements must be taken into account.

Hence, a determination of thyroid enlargement by degrees is to a certain extent conditional, since in mass examinations it is difficult to evaluate properly the pathological significance of each thyroid enlargement. The significance can be properly evaluated only as a result of analysing the data of the examination of the organism as a whole and of the thyroid itself, i.e., the degree of its enlargement, shape, function, spatial relation to adjacent organs and an analysis of a number of other symptoms. Dynamic examinations of the population are of great importance in studying the distribution of goitre. It is established in some instances that in a number of persons the pubertal thyroid enlargement of I and II and even III degrees, far from progressing, subsequently disappears without any medication. In these cases it may be confidently said that such an enlargement of the thyroid is a physiolog-

ical phenomenon and not an initial symptom of the disease. In other cases, however, this enlargement at some period already signifies the beginning of endemic goitre.

The most detailed information about the distribution of goitre throughout the world is given by Kelly and Snedden in the bulletin of the World Health Organisation. These authors point out that endemic goitre is found in all the five continents. According to their data, there are now about 20,000,000 patients with goitre in the world. But this figure apparently includes all persons with invisible goitre or with the I and II degrees of thyroid enlargement and hence it evidently should be regarded as insufficiently conclusive. In any case, we can agree with the statement of Kelly and Snedden that there is almost no country where this disease does not occur. Most of the endemies are moderately severe. In some countries there are areas of high endemicity with manifestations of cretinic degeneration.

Areas of high endemicity are found in the United States, Brazil, Switzerland, Nigeria, Cameroun, the United Arab Republic, the Congo, India, Pakistan, Burma, Indonesia and other countries. During the First World War the examination of 2,510,701 men in the United States revealed that about 12,000 had simple goitre, and in 31 per cent of them the goitre caused such thickening of the neck that made it hard to button the collar of the uniform (Kelly and Snedden). But in many of these countries and also in other countries where iodine prophylaxis is practised the incidence of goitre has declined and the severity of its clinical manifestations has been ameliorated substantially. But in countries where antigoitre measures are lacking the number of patients with goitre remains considerable. For example, in such a small country as Finland which has a population of 3,200,000, up to 3,000 patients are operated annually for goitre. Here for every 1,000 of population 141 people

have a goitre and 91 of them even a nodular goitre (Kelly and Snedden). In Mexico over 2,000,000 out of the total population of 10,000,000 have goitre and in Sweden 300,000 out of 7,000,000; in Italy 10 per cent of the population have goitre, etc. In addition to Switzerland, endemic goitre in Europe is also found in Italy, France, the Carpathian area, particularly in Rumania, Czechoslovakia, and also Poland and Albania. In Asia goitre is found chiefly in the Western provinces of China and India, especially in Kashmir. There is information that at one time there was substantial endemic goitre in Mukden Province of China where, however, it disappeared almost entirely because the population started to eat iodine-rich grass or sea cabbage and edible algae.

In 1920, Eggenberger compiled a schematic map of the distribution of goitre in all five parts of the world, including the U.S.S.R., which gives a general idea of the goitrogenous regions.

In the past there were high endemicity areas in the Soviet Union in which 30 to 50 per cent of the adult population and 60 to 70 per cent of school-age children had goitre. At present there are no large goitrogenous areas in the territory of the U.S.S.R.

The distribution of endemic goitre is governed by definite laws. In various parts of the world endemic goitre reaches the greatest distribution in high mountain areas deep in the continent and is met more seldom in the adjacent foothills and valleys. But endemic goitre can also be found along river watersheds or in marshy and forest localities, particularly with podzol soil.)

Closer to the sea the incidence of endemic goitre gradually declines and disappears near the sea, although some goitrogenous districts are also known relatively near the sea coast, particularly in areas with abundant atmospheric precipitation, soil erosion and the proximity of soil waters. Goitre as a mass disease is usually absent in areas with chernozem soils. In high mountain areas

goitre is often accompanied by hypothyroid phenomena and cretinism. In flat country, quite the opposite, symptoms of hyperthyroidism are more frequent, although everywhere endemic goitre, as a rule, does not cause big disorders of the thyroid function and is called euthyroid goitre.

Pathohistology

The present-day classification and conceptions of the pathological anatomy of goitre are based on the knowledge of the morphological and physiological age changes of the thyroid among the population in goitrogenous areas and non-goitrous regions.

The weight of a normal thyroid fluctuates, according to Arndt, depending on the age, from 2 to 35 g. The thyroid of new-born infants weighs about 1 g; between the 11th day and 6 months it does not exceed 2 g; between 6 months to 1 year it reaches 3 g; between 1 year and 2 years—4 g; between 3 and 4 years—7 g; between 5 and 10 years—10 g; between 11 and 15 years—15 g; between 16 and 20 years—25 g; 21 years and older—35 g. These figures do not reflect the degree of swelling of the thyroid during the period of sexual maturation.

But in goitrogenous regions its normal weight is considerably higher. It is known that the so-called live weight curve (Aschoff) of the normal thyroid changes in conditions of a district unfavourable as regards endemic goitre. The fluctuations in the weight of the thyroid stand out more clearly. In endemic goitre regions the weight of the normal thyroid reaches 40 to 50 g. For example, the average weight of the thyroid among inhabitants of different Soviet cities varies as follows: Kharkov, 19 g; Moscow, 19,3 g; Baku, 20 g; Yerevan, 21 g; Leningrad, 24.5 g; Perm, 29 g; Tbilisi, 32 g; Irkutsk, 53 g; Alma-Ata, 48.1 g; Dushanbeh, 39.6 g. In Fribourg, Switzerland, where goitre

was very widespread, the weight of the thyroid reached 71.3 g. On the other hand, in Kiel, which is free of goitre, the thyroid weighed 26 g.

Small adenomas are at times found in the tissue of a normal thyroid; in non-goitrous areas they seldom occur and do not reach a large size. In goitrogenous regions they are found more often and grow more swiftly, at times reaching the size of an infant's head, i.e., turn into a typical nodular endemic goitre.

The histogenesis of goitre has been carefully studied by a number of authors, in particular by Aschoff and Wegelin and by B. V. Alyoshin in our country. The interconnection between structure and function can be seen in the development of the thyroid. Among the population in high mountain alpine areas the thyroid preserves the embryonal type of structure for a longer time, while among inhabitants of flat country with a strong mineralisation of drinking water and food products the thyroid acquires a mature macrofollicular colloid structure more swiftly (O. V. Nikolayev). Correspondingly, in alpine districts hypothyroidism occurs more often, while in the plains hyperthyroidism is more frequent. The thyroid develops through the proliferation of the epithelium in the form of so-called Sanderson's pillows, which evaginate into the follicles. As new capillaries and nerves penetrate them, new follicles are formed. The existence of proliferating processes and growing Sanderson's pillows are a sign of the growth of thyroid tissue. Along the periphery of the thyroid the follicles might reach 300-500 mu in size. The absence of proliferative phenomena is characteristic of the stationary condition of the thyroid. The shape of cell elements which normally are of a cuboid form and the state of the colloid give an idea of the activity of the thyroid tissue, but only to a certain extent. In recent years studies of the thyroid structure and function have been made with the aid of radioactive iodine by the method of radio-autography.

The adenomas arising in the thyroid are encapsuled and to some extent duplicate the structure of the normal thyroid tissue, i.e., they can have a varying degree of maturity, from parenchymatous to micro- and macrofollicular colloid structure. A similar structure is repeated in various forms of endemic goitre. One should bear in mind that destructive processes and also a number of secondary alterations easily develop in the adenomas.

Two main pathohistological forms of structure of endemic goitre should be singled out: diffuse and nodular, or adenomatous, goitre. The third form is a mixed goitre. All these forms are divided for their histological structure into parenchymatous and colloid; the latter are divided into micro- and macrofollicular, depending on the degree of maturity.

The less mature parenchymatous goitre is divided into trabecular, tubular and microfollicular. A goitre can be proliferating and stationary. In nodular goitre secondary destructive alterations cause haemorrhage, fibrosis, the formation of cysts, calcification, etc. Blastomatous processes with a typical and infiltrating growth easily arise in nodular goitres, i.e., the adenomas degenerate into malignant neoplasms. Among the latter is cancer, the most frequently encountered malignant tumour, hemangio-endotheliomas and sarcomas. The latter are very rare. The disposition of nodular goitre to malignant degeneration attests to the correctness of Aschoff's view, now recognised by an overwhelming majority of authors who regard a nodular goitre as a blastoma, i.e., a benign tumour. The higher the endemicity of a region, the more often malignant goitre occurs there. The question of nodular goitre should be examined in the aspect of an oncological problem.

The classification of A. I. Abrikosov, B. N. Mogilnitsky, P. V. Sipovsky, Wegelin, Aschoff and Arndt is quite satisfactory at the present stage of study of the pathohistol-

ogy of endemic goitre. We give below the classification of Abrikosov-Arndt which reflects the diversity of goitre structure. We omit from this classification some forms which are not directly connected with endemic goitre; at the same time we supplement this classification by indicating the size of the follicles in microns.

A. Diffuse goitre (hyperplastic)

I. Diffuse colloid goitre. 1. Microfollicular with the predominating size of follicles up to 20-30 mu. 2. Microfollicular with follicles of normal size or increased to 70-150 mu and more: a) non-proliferating; b) proliferating.

II. Simple diffuse parenchymatous goitre.

III. Basedowicated diffuse goitre.

B. Nodular goitre (adenomatous)

I. Nodular colloid goitre: 1) non-proliferating; 2) proliferating.

II. Simple nodular parenchymatous goitre: 1) microfollicular adenoma; 2) trabecular adenoma (Fig. 23); 3) tubular adenoma (Fig. 24).

III. Regressive forms of degeneration of nodular goitre.

IV. Basedowicated nodular goitres.

C. Mixed diffuse and nodular goitre

I. Colloid diffuse and nodular goitre: 1) microfollicular (Fig. 25); 2) macrofollicular non-proliferating; 3) macrofollicular proliferating (Fig. 26-27).

II. Parenchymatous diffuse and parenchymatous nodular goitre.

III. Colloid and parenchymatous combined (and degenerative) forms.

IV. Basedowicated mixed goitre (diffuse-nodular) (Fig. 28).

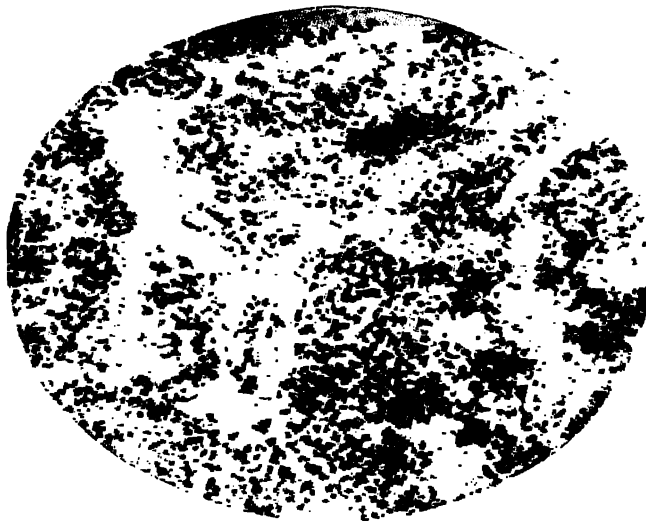

Fig. 23. Parenchymatous goitre of trabecular structure.

Fig. 24. Parenchymatous goitre with sections of an adenoma of tubular structure.

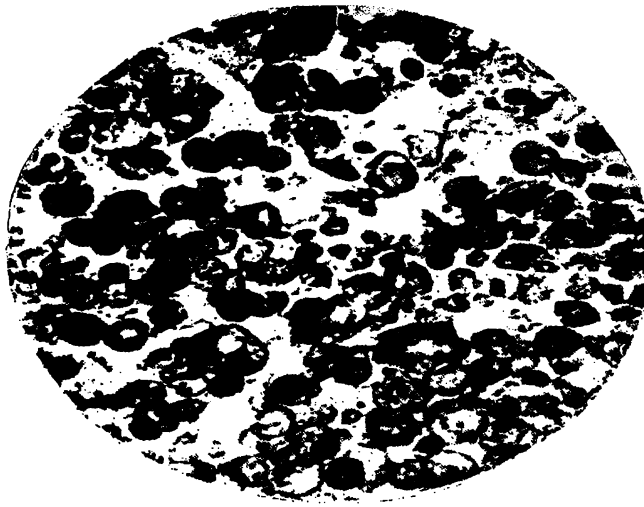

Fig. 25. Microfollicular colloid goitre with considerable development of interfollicular connective tissue (fibrous goitre, formed in connection with the development of regressive phenomena).

Fig. 26. Macrofollicular colloid diffuse goitre with small proliferative phenomena and vacuolisation of the colloid.

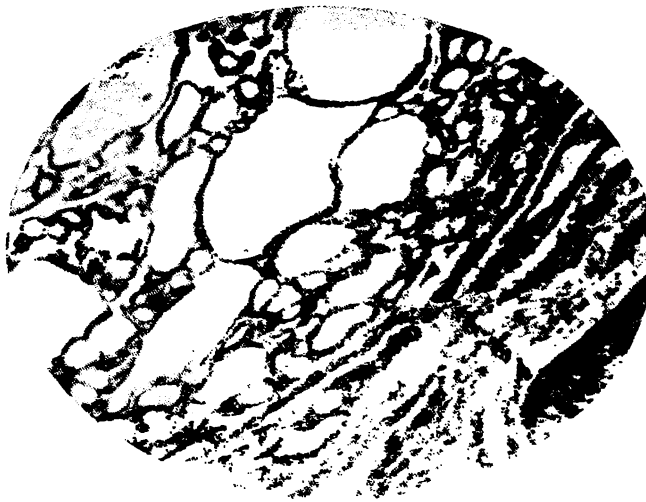

Fig. 27. Section of a wall of a nodular macrofollicular colloid goitre.

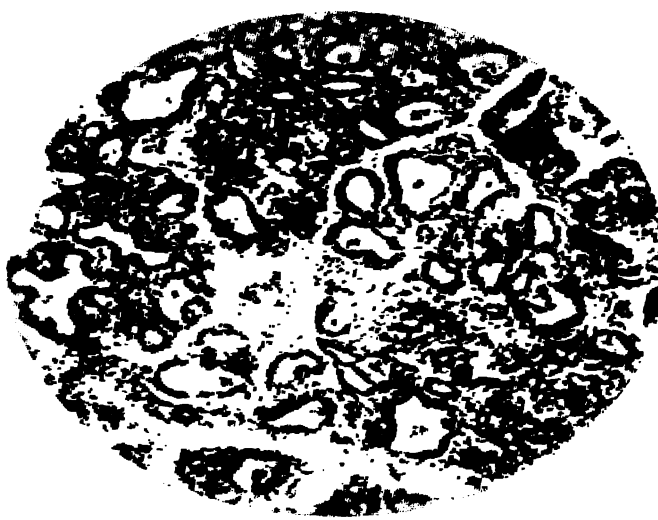

Fig. 28. "Basedowicated" microfollicular colloid nodular goitre. Formation of star-shaped follicles and lymphoid infiltration in interfollicular tissue. Liquid colloid slightly stained by eosine.

Fig. 29. Proliferating papillomatose nodular goitre with infiltrating growth and presence of a big number of cells with mitosis in the nuclei (goitre malignisation).

D. Conglomerative nodular and diffuse colloid goitre.

I. Proliferating (Fig. 29)
II. Non-proliferating

Such a diversity in the pathohistological structure of endemic goitre could give rise to suppositions about differences in the aetiology and pathogenesis of these forms of goitre. But a supposition about the different aetiology of endemic goitre in various geographical areas is groundless. On the contrary, a study of the pathohistology of endemic goitre reinforces the view of this pathology as a specific single disease, the definition of which was given at the beginning of this chapter. In each goitrogenous region its pathohistology has its distinctions that depend on the diversity of the external and internal conditions which influence the main factor causing endemic goitre and its action.

In conclusion it should be noted that the term "parenchymatous goitre", which is frequently used, should be applied only to the histological structure of the goitre, since in the clinical study it is often difficult to determine what goitre the patient has—parenchymatous or colloid, macrofollicular or microfollicular. That is why in clinical conditions it is necessary to determine only the form of the goitre and not its pathohistological structure, i.e., it is necessary only to establish whether it is diffuse or nodular goitre.

Histological investigations, with the aid of special stains, of the intrathyroid innervation of endemic goitre (Y. I. Tarakanov, M. M. Alikishibekov and others) and also autoradiographic examination of goitres removed in an operation make it possible to study the finest changes in the innervation of the thyroid, differences in the uptake of radioactive iodine by the tissue of the thyroid, whose function may be sharply altered, and graphically to demonstrate the varied picture in different parts of the goitrously degenerated tissue (R. K. Islambekov and others). Pathohistological studies of goitre help correctly to understand its pathogenesis and aetiology.

Aetiology and Pathogenesis

Knowledge of the aetiology and pathogenesis of endemic goitre is of great importance for understanding the essence of the disease and for its treatment and prophylaxis. A considerable step forward in the study of the aetiology of endemic goitre was made over 100 years ago when Prevost and Chatin (1849-1850) formulated a harmonious scientific theory, connecting this disease with iodine deficiency in nature and the action of a number of secondary or additional factors; in particular, they indicated the unfavourable social and living conditions. This theory was not developed and supported and, moreover, its social significance was gradually reduced to nought.

Nevertheless, this theory had a great many followers. Most of them, however, spoke only about the importance of iodine deficiency, ignoring other factors which, according to this theory, might influence the origin of endemic goitre.

Many other theories appeared concerning the origin of endemic goitre, associating its development with the quality of drinking water, geological formations, the influence of various metals and chemical elements, the biological specific features of the organism, helminthism, contamination with special gregarines, avitaminoses and with other factors. A special place was taken by the theory of the infectious toxic origin of goitre put forward by McCarrison. This theory pointed to the importance of sanitary factors, to the role of soil pollution, to the great significance of unfavourable sanitary-hygienic living conditions of the population, which actually attracted the attention of many investigators.

It should be noted that each of those theories was corroborated by definite data, which subsequently served as material for broad generalisations and the formulation of the contemporary leading theory of endemic goitre genesis.

Our conceptions, based on the synthesised experience of the study of the goitre problem in its historical aspect and the materials obtained in most of the major goitrogenous regions of the Soviet Union, the latest data on the physiology of the thyroid and the proper understanding of the unity of the organism and the environment, make it possible to delve into the substance of questions related to endemic goitre, to learn the main general laws governing its development. The unusual complexity of the changing interrelations of the organism and the environment in the diverse conditions of goitrogenous areas makes it very difficult to examine these relations comprehensively. Nevertheless, taking into account the most essential connections of endemic goitre and the laws governing its development and treating it as a definite nosological unit, it is possible not only to establish the leading cause of

the initial form of the pathological process, but also to study the pathogenesis of endemic goitre by phases of its development and course in various geographical areas and in patients of the one and the same area. In this respect, the initial phase of endemic goitre development requires close attention. Thus, specific diffuse hyperplasia of the thyroid which is of a mass character among the population in a goitrogenous region is the main outward sign of changes taking place in the whole organism in the specific conditions of any goitragenous area. Therefore, to solve the problem of the genesis of endemic goitre it was necessary first of all to establish the reason for this thyroid enlargement and the general elevation of its weight curve among various age groups in goitrogenous regions.

Extensive endemiologic and experimental investigations have shown that hyperplasia of the thyroid in goitrogenous regions undoubtedly has the nature of a compensatory reflectory reaction of the organism to factors of the external environment, particularly iodine deficiency.

If the organism overcomes the changes in metabolism caused by iodine deficiency and the thyroid is not enlarged or even if it is enlarged but subsequently this enlargement does not progress, there is every ground for speaking of a "physiological measure" (Pavlov) of protection against the disturbances in iodine metabolism. If, however, there is a stable derangement in the compensation of the alterations that arise in the organism, the reaction is no longer limited to simple hyperplasia of the thyroid but goes over into specific goitrous hyperplasia as a manifestation of the disease of the entire organism.

It is now generally recognised that iodine deficiency, found in certain districts or, as Vinogradov puts it, in biogeochemical provinces, is important for the aetiology of endemic goitre. In these districts the daily influx of 200-220 gamma of iodine into the organism with food and water is reduced to 80-20 gamma. As a result, altera-

tions of the iodine exchange and a deficiency of the thyroid hormone arise in the organism, which affects the age-weight curve of the thyroid. It is in this environment that an endemic goitre might develop. An important part in the pathogenic action of iodine deficiency as the causal factor in the development of endemic goitre is played by endogenic and exogenic conditions which turn the possibility of endemic goitre into reality.

These and some other special conditions and factors can create a relative iodine deficiency in the organism or insufficient production of the thyroid hormone even when the influx of iodine is normal. Intoxications of diverse origin are of great importance among the conditions which facilitate the action of the causal factor in the development of the disease; they are also of essential significance in the pathogenesis of some of its separate forms and manifestations. These intoxications may be connected with bad sanitary-hygienic conditions, poor quality of drinking water, irrational and monotonous diet poor in vitamins and some substances which the organism needs, and, lastly, infectious diseases. Changes in the organism connected with the sexual maturation period also promote the diseases; it develops most frequently in women. Thyroid enlargement in connection with pregnancy was noticed long ago.

Although an endemic goitre might begin at any age, the greatest incidence is seen in children between 10 and 12 years of age. After 20 or 30 years the incidence of goitre declines, particularly among men. It is interesting that the difference in the frequency of goitre among girls and boys, relatively little pronounced at an early age, becomes noticeable in the sexual maturation period and subsequently is even more strongly manifested among adult men and women.

Account should be taken of the important physiological interrelations between the female sexual glands and the thyroid. Periodic changes connected with the ovary-men-

strual cycle, pregnancy, climacteric period and also diseases of the genital sphere which are frequent among women and are accompanied by alterations of hormonal function of the ovaries, cannot but affect the condition of the nervous system, the thyroid and the stability of the entire organism. Experience shows that these factors facilitate the development of endemic goitre.

In the study of goitre attention has been paid to the frequency of the disease in definite families, which raised the question of the role of heredity in the development of goitre. For a long time this question was incorrectly approached since the exceptional importance of the living conditions of the families concerned was ignored. The genealogical method which does not take account of the real aetiology of endemic goitre was applied here one-sidedly. Nevertheless, the question of its familial nature raised a long time ago has by far not been studied adequately to judge the role of hereditary factors in the aetiology and pathogenesis of goitre. The only thing that is convincing is data on goitre in monozygotic and dizygotic twins.

These data were cited by Siemens who noticed that when there was pronounced goitre or an enlarged thyroid in one of the monozygotic twins there were similar changes of the thyroid in the other twin. This applied to the prevalence of one or another lobe, the size of the goitre and its location. On the contrary, in a study of dizygotic twins similarity in the location and size of the thyroid was seen less frequently, while in some of the dizygotic twins these correlations were entirely different. Investigations in which the genealogical method is used offer only certain grounds for speaking about the reactivity of the organism of man formed under the influence of a complex of endogenic and exogenic factors, but not of hereditary predisposition to endemic goitre or the inheritance of some kind of goitrogenous factor. It is in this light that

genealogical data collected in endemic goitre areas should be evaluated.

It is beyond dispute that when a family moves from a goitrogenous area to a non-goitrous region, the goitre in members of the family often begins to involute and subsequently the new generation in this family becomes healthy. The same is seen in case of iodine prophylaxis when parents with goitre give birth and raise healthy children without any signs of thyroid enlargement, notwithstanding the fact that they continue to live in a district potentially dangerous as regards endemic goitre. Consequently, iodine prophylaxis improves the health of the population. This strikes a powerful blow at the views and opinions expressed at times that endemic goitre is inherited.

The influence of sanitary-hygienic conditions on the distribution of goitre was noticed long ago. Many studies of the importance of sanitary-hygienic factors and infectious toxic influences and investigations designed to discover the pathogen of goitre acting through the intestinal tract have been made by a number of researchers, chiefly McCarrison. But all attempts to find a pathogen of goitre were in vain. M. P. Izabolinsky (1910) by precise investigations, meeting the requirements of microbiology, proved that endemic goitre is a non-infectious disease, unconnected aetiologically with a toxic factor. But the experimental observations of McCarrison can be successfully used for demonstrating the importance of conditions which intensify the action of the causal factor of endemic goitre.

This was also found by us in a study of goitre in Samarkand, Uzbekistan, in 1930. The old way of life of a country which had been a colony still made itself felt and we succeeded in establishing very strikingly the role of the social and living conditions in the incidence of goitre. Thus, for example, in the old part of Samarkand where at that time the sanitary-hygienic conditions were extremely

unfavourable, the drinking water was polluted and the dwellings were very primitive and overcrowded, the incidence of goitre among school children was considerable. The frequency of insignificant thyroid enlargements was the same for both sexes in the old part of the city and in the new where the living conditions were different, the supply of water was much better and purer and the population lived in more hygienic conditions. But the frequency of thyroid enlargements of the III and IV degrees in these areas sharply differed. In the old part of the city goitre was found in 24.8 per cent of the boys and 28.5 per cent of the girls, in the new part of the city only in 4.4 per cent of the boys and 10.3 per cent of the girls.

McCarrison, having established the different incidence of goitre among Britons and local inhabitants in the Himalayas, noted the greater incidence of intestinal infections among the latter and looked for ways of combating goitre in intestinal antiseptics and a change in the water supply sources. But it is perfectly clear that here the primary part was played above all by the causes which gave rise to unequal living conditions among different groups of the population in the Himalayas, and it is this that determined the difference in goitre incidence. That this is really the case is demonstrated by the sharp decrease of goitre incidence among pupils, particularly of technical schools and general schools, in the new Samarkand in connection with the improved sanitary-hygienic conditions and mode of life. This was noted by us as far back as 30 years ago.

Many authors explain the greater development of goitre by the presence of huminous substances in drinking water. Not long ago S. V. Maximov, and also Y. V. Sidorenko and P. S. Pakhotina (1957) pointed out that methylthiouracil elevates the strumogenic effect.

The significance of the social and living conditions in the aetiology of endemic goitre was stressed already by Chatin (1849), the author of the iodine deficiency theory. He drew attention to the role of unsanitary conditions,

poor diet, poor quality of drinking water, with which an infectious toxic influence on man's organism is associated. But Chatin considered these factors as additional causes of endemic goitre. Unfortunately, Chatin's theory was subsequently distorted and only the conception of the role of iodine deficiency in nature as the sole cause of goitre became associated with his name. In effect, numerous experiments of McCarrison, which are of great interest, merely confirm the importance of living conditions for the strumogenic action of iodine deficiency. This applies to his experiments on pigeons which received the same food but were kept in different tiers of the cages, experiments on goats in which a goitre was induced merely by keeping them in unsanitary conditions, experiments on fish and experiments on men in which polluted water was used. We must stress that experiments on people are impermissible and that their results cannot be considered as proof, inasmuch as the non-specific bacterial intoxication produced not a picture of endemic goitre, but a clinical picture of thyroiditis with enlargement of the thyroid and its normalisation when the experiments ceased. Moreover, these experiments were conducted in a locality with a soil extremely poor in iodine, but the drinking water was obtained from iodine-rich sources.

McCarrison noted that the filtration of water through a Berkefeld filter or its boiling did not provide a full guarantee against the disease, which refuted the reliability of his conclusions about the role of the infectious toxic factors. He thought that the possibility of infection from the soil could not be ruled out. He also conducted experiments on dogs and rats, using a filtrate from faeces emulsion of people with goitre and from cultures of anaerobic bacteria. He succeeded in inducing a goitre experimentally. But his conclusions that this goitre was passed on to the progeny of the test rats and that there was experimental "cretinism" and lesion of the parathyroid glands in some animals can hardly be considered conclusive. His

assertion that a number of disinfectants used for intestinal antiseptics (salol, thymol, benzonaphthol) and changes in the intestinal flora favourably affect the course of experimental goitre and goitre in people are not proof of the importance of the infectious genesis of endemic goitre. It should be noted that already in 1937 McCarrison wrote that iodine deficiency was the only known cause of endemic goitre.

And so, admitting the role of infectious toxic factors, we must not regard them as the leading, specific or determining ones in the development of goitre. Indeed, in the high mountain area of Kabarda, in villages which use water of glacial origin, the water was of excellent quality, in the sanitary sense. It must have been the same in the past and nevertheless nodular goitre was widespread in these villages owing to iodine deficiency. On the contrary, in a number of districts with unfavourable sanitary-hygienic conditions and drinking water of poor quality, with the undoubted presence of infectious toxic influences, helminthism and so on, but in the absence of the specific factor of goitre development, i.e., iodine deficiency, no goitre endemy was observed.

As for the mechanism of action of non-specific infectious toxic factors, here evidently there is usually the decreased stability of the organism or a change of its reactivity owing to an alteration of the function of the nervous system, particularly the trophic function. This undoubtedly must reflect on the entire endocrinal system and particularly on the hormonal function of the thyroid and the absorption of iodine by it, i.e., iodine metabolism. Interesting data in this respect have been obtained by Strongina in Yaroslavl. She found a greater incidence of goitre among children which had been sick with infectious diseases. She convincingly explains the facts she obtained in the light of present-day physiology from the positions of nervism. Infectious toxic factors influence the development and the course of goitre and have no less

importance in its pathogenesis than in its aetiology. Moreover, there are reasons for assuming that the worse the sanitary-hygienic conditions, the greater the infectious toxic influences, the more frequent nodular forms are found among the various types of endemic goitre. More than that, changes of the nodules in the process of goitre development likewise are more frequent in unfavourable sanitary-hygienic conditions. Evidently, the infectious toxic influences associated with these conditions, acting through the nervous system, change the trophics of the tissues and promote destructive processes in the thyroid and particularly in the nodules of the goitre. Nodular goitres, removed by us in operations, were marked by a great diversity of the regressive changes associated with destructive processes.

In experimental conditions a goitre can be induced under the influence of numerous factors, particularly chemical factors. A strumogenic effect was obtained, even with the normal influx of iodine into the organism, by changing the thyrotropic function of the hypophysis or inhibiting hormone production in the thyroid of animals. Numerous recent investigations have shown that substances of the thiourea (thiouracils) PASK, thiocyanates and many other antithyroid substances also act this way. It is interesting that a decline in the iodine content of the soil as a result of its extraction by some trees has been observed in endemic goitre districts (Kelly and Snedden).

Among the various chemical factors influencing goitre development special importance is ascribed to calcium salts. In our country this viewpoint was especially supported by M. Y. Shwartsman, but he pointed out that the geographic distribution of goitre must not necessarily be connected with some definite geological formations. Still earlier a number of authors also pointed to the role of calcium in the origin of endemic goitre. But such a viewpoint cannot be considered correct. A number of experi-

mental data has been cited to prove the connection between the action of calcium salts and the development of goitre. Indeed, in experimental conditions, a thyroid enlargement in rats and pigeons, with a picture of parenchymatous hyperplasia, can be obtained by adding calcium to the usual food. But on closer examination it was established that calcium is not an aetiological factor of goitre. There are large territories with soils and strata rich in calcium that are absolutely free from endemic goitre. And quite the reverse, in high mountain alpine districts where goitre is widespread there are soils and waters poor in calcium salts and with a very low content of salts in general. Gradually, as the water flows away from the sources of mountain rivers, it is enriched in salts and the soil also becomes more mineralised, while endemic goitre, far from growing, becomes weaker or disappears.

A study of the role of calcium in the aetiology of endemic goitre should be made with account of its biological significance in the process of development and vital activity of the organism, specifically its importance for the function and development of the neuro-endocrinal system. A comparison of special experiments on rats, when the influence of potassium and calcium salts on the thyroid was studied (O. V. Nikolayev and N. S. Lebedeva), showed that these cations, all other conditions of the experiment being equal, cause specifically distinct alterations in the structure of the thyroid in growing animals (rats). Thus, in experimental iodine deficiency which induces a goitre, changes in the proportion of ions of potassium and calcium, if calcium relatively prevails, cause sharp hyperplasia and hyperfunction of the thyroid and the formation of a high epithelium and faintly stained colloid. If potassium prevails hyperplasia is less pronounced, the epithelial cells are less differentiated, they are large and of cuboidal form; the follicles, however, are small, they contain no or little colloid and for their struc-

ture resemble embryonal tissue or tissue of a microfollicular and parenchymatous goitre. Calcium exerts considerable influence on the size of the goitre in conditions of an experiment with iodine deficiency. Indeed, this factor intensifies the formation of an experimental goitre caused by iodine deficiency. Taylor saw a sharp elevation of hyperplasia of the thyroid in rats when calcium carbonate was added to iodine-poor food. At the same time he noted a big uptake of radioactive iodine by the thyroid. N. S. Demidenko, S. V. Maximov, Straube, and others also hold that calcium merely intensifies the reaction of the thyroid to iodine deficiency.

In a number of goitrogenous regions we were able to notice long ago that in the same conditions of iodine deficiency the goitre in people reaches much larger dimensions in areas with well mineralised soil and hard water. On the other hand, in localities poor in salts, usually the goitre is not of large size. But the pathogenesis of goitre in conditions of iodine deficiency and the action of the above-mentioned factors is of particular interest. Thus, a comparison of the picture of microfollicular alpine goitre and the goitre of new-born infants with microfollicular experimental goitre obtained under the influence of iodine deficiency in combination with calcium, suggests that parenchymatous and microfollicular (colloid) forms of goitre are the less mature ones. De Quervain already pointed to the different histological structure and clinical manifestations of goitre in various geographical areas. McCarrison also had no doubts that this depends on the altitude of the endemic goitre district above sea level, the nature of the soil, the hardness and composition of the water, the conditions of social and personal hygiene, the food ration and the composition and quality of the foodstuffs.

The correlation between potassium and calcium plays an essential part in the development of the normal thyroid and in the transition from its embryonal parenchy-

matous structure to the mature macrofollicular colloid structure. Mineralisation of the food influences the main microscopic forms of endemic goitre. Naturally, the above-indicated correlation of the ions of potassium and calcium in nature and in the food does not exhaust the intricate influence on the organism exerted by various physico-chemical factors, but in any case the influence of calcium salts may be regarded as one of the components in the aetiological factors of endemic goitre, largely affecting the structure of the goitre as well.

Inasmuch as the nervous system plays the leading part in the interrelations of the organism and the environment, its exceptionally great importance in the aetiology and pathogenesis of various forms of endemic goitre should be expected. First of all, the physiological function of the thyroid, whose activity largely depends on the influx of iodine into the organism, is regulated by the nervous system. Evidently, the processes of compensation of the insufficient iodine balance, specific for the population living in an endemic goitre district, depend on the state of the nervous system and the regulating influence it exerts on the function of the endocrinal system.

The great importance of central cortical regulation in processes of adaptation of the organism to diverse conditions of life and in the compensation of disturbances that arise in metabolic processes has now been demonstrated by numerous facts obtained in experimental pathophysiological and physiological studies and also in clinical observations. Intricate reflectory processes which compensate alterations of iodine metabolism arising in the organism in a goitrogenous region depend on the level of metabolic activity or the tonus of the cerebral cortex and the type and nature of the nervous processes. It was known long ago that even in areas of high endemicity a great many people remain healthy, notwithstanding the sharp decrease in the influx of iodine into the organism. Diverse organs and systems take part in the intricate re-

flectory reactions which are also connected with the activity of the substratum of the reacting organ subjected to the action of iodine deficiency. Here it is in place to recall the words of K. M. Bykov who wrote: "The harmonious combination of factors of the outside world with the internal environment is effected by the metabolic nerves, to use the accepted terminology, the trophic nerves."

When we picture to ourselves the action of iodine deficiency on the organism we must take into account the mechanisms of neurohumoral correlation effected in the higher parts of the nervous system. It is the insufficient physiological compensation or, as Pavlov put it, "physiological measures" against the lower content of iodine in the liquids and tissues of the organism that arises when there is iodine deficiency in nature and corresponding conditions exist, of which we spoke earlier (i.e., infectious toxic influences, disturbance of nutrition, etc.) that lead to the disease. There is no doubt that highly intricate mechanisms take part in the reaction of the organism to external factors of the environment, particularly to iodine deficiency. This reaction is manifested in thyroid enlargement up to the development of a nodular goitre and, lastly, of endemic cretinism. In the process of goitre development, besides the hormonal derangement of the function of the thyroid, its second important service inherent in the internal secretion glands is disturbed, namely, its role as an internal receptor connected, through intermediary instances, with the subcortical centres and the cerebral cortex.

Taking into account the aforesaid, the genesis and development of goitre can be considered in the aspect of the corticovisceral theory of the origin of pathological processes. Local deep morphological alterations which take place in the thyroid in endemic goitre, in their turn, become the source of constant irritation, or pathological afferent impulsation which changes the state and function

of the higher parts of the nervous system. It should be taken into account that morphological alterations of the thyroid tissue in endemic goitre embrace its various parts, especially the nerve network within the gland.

This is proved by the histological studies of experimental goitre of A. Derevisch who observed changes in the Golgi's apparatus in thyroid cells and deep lesions of the nerve elements. Of still greater importance are studies related to the staining of nerve tissue in goitres removed during surgical operations (Y. I. Tarakanov, M. M. Alikishibekov, V. I. Akimov and others).

Changes in the processes of metabolism and synthesis of the thyroid hormones that arise in the organism and at times are difficult to trace in clinical study, do not fit into the simplified scheme of euthyroidism, hyper- and hypothyroidism. Clinically, the state of the organism in endemic goitre is frequently of an euthyroid nature. General changes in the organism become more evident when symptoms of hypothyroidism appear and are accompanied by a clinical picture of cretinism. It is perfectly clear that cretinic dystrophy in endemic goitre represents the most far-gone pathological process. But in the first phase of strumous hyperplasia the same changes, connected with a disturbance of the corticovisceral relations, evidently arise, to an incomparably smaller extent. What is very important is that there are some forms of endemic cretinism without pronounced hypothyroidism. Similarly, in goitrogenous regions one can frequently encounter cases of deafness and muteness and a number of other neuro-endocrinal dysplasias and derangements of higher nervous activity connected with goitrous degeneration. These cases are not explained by simple quantitative deviations in the incretory function of the thyroid. At the same time the aforesaid can explain the particular disposition of adenomatous goitre to proliferative processes and to Basedowication, not to speak of the above-mentioned destruction or degeneration, which leads to a number of secondary pathohistological forms.

It is from these positions that one can undertake to explain the transition of an adenoma as a benign neoplasm to a malignant tumour, cancer, which is encountered more frequently in goitrogenous regions than in non-goitrous areas. Endemic studies demonstrated long ago that there are essential differences in the clinical manifestations of athyroidism, congenital or caused by thyroidectomy, on the one hand, and endemic cretinism, on the other. This can be explained by the fact that in athyroidism there is no signalisation on the part of the interoceptors since the thyroid is absent. In cretinism caused by deep goitrous degeneration of the thyroid, often observed from generation to generation, there are constant interoceptive afferent impulses, which create a distorted regulation of metabolic processes by the corresponding parts of the nervous system, resulting in deep neurodystrophic lesions of various organs and systems. How important this conception is for medical practice is shown by the fact that removal of the altered part of the thyroid tissue or resection of the enucleated goitre in a cretin does not elevate the phenomena of hypothyroidism. The explanation is that by resecting the goitrously changed tissue in the cretin we thereby remove the pathological signalisation. On the other hand, the remaining elements of the slightly altered tissue subsequently undergo certain regeneration, which activates the function of this tissue and causes an improvement in the general state of the organism. Deep alterations in the thyroid tissue of cretins explain the inefficacy of iodine therapy. On the other hand, the introduction of thyroidin into the organism often results in a substantial involution of the goitre and brings about a general improvement in the patient's condition. That is why both treatment with thyroidin and removal of the nodular goitre should always be regarded as pathogenically substantiated therapy. Surgical intervention removes the focus of pathological afferent impulses by the nervous apparatus in the thyroid, which may favourably influence the cortical regulation of the

thyroid function. Optimum conditions are created for a compensation of the alterations in the neuro-endocrinal system existing in the organism and for a reaction to the specific causal factor constantly operating in goitrogenous regions, namely, iodine deficiency.

In conclusion mention should be made of the numerous investigations by B. V. Alyoshin and his colleagues to prove the existence of derangements in the neurohumoural regulation of the mechanism of changes in the thyroid structure and function in the light of the corticovisceral theory. The results he obtained may be used for explaining the pathogenesis of various forms of endemic goitre; nevertheless, we advise against the hasty application of the data of these studies to the clinic of endemic goitre. In assessing the significance of sanitary-hygienic conditions and the diet as well as the influence of a number of concomitant diseases and intoxications which leave a definite trace in the nervous system, account should be taken of the influence of infectious toxic factors on the trophic function of the nervous system, on higher nervous activity. Hence it is clear that in studying the action of various factors on the development of endemic goitre, we must look for their influence not so much on the use of iodine by the organism as on the action exerted, through the nervous system, by iodine deficiency on the thyroid, on iodine metabolism and the synthesis of the hormone needed by the organism.

Consequently, the influence of iodine deficiency on the organism as the cause of endemic goitre is manifested only when the synthesis of thyroxin in the thyroid is limited and it is unable to satisfy the metabolic requirements of the organism in this hormone. At present the proposition on the aetiological importance of iodine deficiency has not only been firmly established, but is also generally recognised. The three main propositions, put forward by Chatin in 1849, remain basically immutable to this day, although they require certain corrections and amendments. The first is that goitre and cretinism are unknown in normally

iodised areas; second, that these diseases arise when there is a relative decrease in the quantity of iodine consumed; and third, iodine is a specific remedy in combating goitre.

Assuming a causal dependence between endemic goitre and iodine deficiency in nature, Chatin pointed out that the development of goitre, in addition to this main factor, is facilitated by a complex of factors, which he called additional moments. Among them are: crowded, dark, poorly ventilated and unsanitary living quarters, dirty clothes, insufficient nutrition, drinking water of poor quality, inadequate wind in unfavourably situated mountains, sex, age, temperament of people, etc. At the time when Chatin put forward his theory there was no adequate knowledge of the physiological importance of iodine for the organism, nor was the hormonal function of the thyroid known then. This impeded the success of Chatin's theory and its proper understanding. Iodine prophylaxis was undertaken with big doses, which led to a number of failures and made doctors wary of applying in practice Chatin's theoretical propositions. But study of the aetiology of endemic goitre continued. The introduction of analytical chemical methods provided the opportunity to establish more precisely the content of iodine in the tissues of the organism and in the environment. When Fellenberg's studies of the iodine content of a number of foodstuffs, the soil and mountain rocks, the air, water, etc., were published in 1926, when the main laws of iodine metabolism were established, the importance of iodine deficiency in the aetiology of goitre appeared in a new light. Unfortunately, at that time other theories of the genesis of endemic goitre prevailed, specifically the theory of the infectious toxic origin of goitre, in view of which there were great differences among investigators of the goitre problem and this prevented the organisation of co-ordinated antigoitre measures in a number of countries.

In 1930-1931, having examined the experience in studying the problem of endemic goitre and critically analysed the numerous experimental, clinical and also pathomorphologi-

cal and endemiological data available, we started to check the correctness of the iodine deficiency theory of Prevost and Chatin in various goitrogenous regions of the Soviet Union not only by means of diverse investigations, but also in the practice of combating goitre. In so doing we took into account all the preceding extensive experience of Soviet investigators who worked in different goitrogenous regions, particularly the results of the later investigations by A. P. Vinogradov who studied the biogeochemical provinces of the Soviet Union noted for a surplus or deficiency of various trace elements, iodine included. All these data corroborated the correctness of our conceptions. As for the aetiology and pathogenesis of endemic goitre based on the iodine deficiency theory, we shall cite only some data of foreign and Soviet investigators of interest in this respect. Thus, if the content of iodine in the air at sea level is taken as 100 per cent, its content at different altitudes is shown in Table 1.

Table 1

Content of Iodine in the Air at Different Altitudes Above Sea Level (after Fellenberg)

Altitude (metres)	Iodine content (per cent)	Altitude (metres)	Iodine content (per cent)
0	100	2,000	14.0
50	94.8	2,500	8.6
100	90.3	3,000	5.3
250	78.1	3,500	3.2
500	61.1	4,000	2.1
1,000	37.5	4,500	1.2
1,500	22.9	5,000	0.7

At an altitude of 1,000 m the air loses 62 per cent of the iodine and at an altitude of 5,000 m the content of iodine in the air is negligible and is less than 1 per cent of that at sea level. The movement of the atmosphere, wind and other conditions of the environment and also the presence of various substances which influence iodine compounds, change these correlations. In general the content of iodine in nature is uneven not only in geographical areas

far removed from each other, but even within the range of scores of square kilometres or a few hundred metres of altitude. The weather, the season of the year and the direction of the wind influence the iodine content of water of different supply sources. The iodine content fluctuates sharply in plants, particularly algae. For example, in fresh-water algae the content of iodine ranges from 200 to 800 gamma per 1 kg; in sea algae its content varies from 5,000 to 900,000 gamma per kg of dry substance. In fresh-water fish the quantity of iodine runs from 40 to 70 gamma per kg of flesh, while in sea fish it reaches 140-1,400 gamma per kg (after Fellenberg). In edible algae or in sea cabbage the content of iodine might reach up to 2,000,000 gamma and more per kg; in Greek sponges, up to 3,870,000 gamma per kg of dry substance. The iodine content in foodstuffs of plant and animal origin also fluctuates sharply.

According to Fellenberg, cocoa contains 80 gamma/kg of iodine; coffee, 80 gamma/kg; milk, from 40 to 70 gamma/kg; butter, 50 to 106 gamma/kg; eggs, from 12 to 80 gamma/kg. Refined cod liver oil contains 3,520-7,200 gamga/kg of iodine; beef, 53-71 gamma/kg; liver, 19-87 gamma/kg. The tissues and organs of bulls and cows have the following quantities of iodine: thyroid, 228,000 gamma/kg; myocardium, 73 gamma/kg; liver, 57 gamma/kg; spleen, 140 gamma/kg; testicles, 55 gamma/kg; the lungs and adrenals contain no iodine.

R. S. Kagan and R. Y. Kaznachei have measured the content of iodine in the foodstuffs in some areas of Transcarpathian Ukraine which are unfavourable as regards the incidence of endemic goitre. Calculations of iodine content per kg of foodstuffs are as follows (Table 2).

The structure of the soil and its specific features influence the iodine content in foods. This has been established by the studies of A. P. Vinogradov and V. V. Kovalsky. According to Vinogradov and his co-authors, in high mountain areas and in flat country endemic goitre exists primarily in the zone with podzol or similar soils. There

Table 2

Content of Iodine in Gamma per Kilogram of Foodstuffs

	Endemic goitre region	Non-goitrous region
Semolina	21	—
Buckwheat	62	—
Pearl-Barley	84	—
Flour, 96 per cent	24	65
Oats	38	101
Barley	42	116
Potatoes	46	182

is a strict correlation between iodine content in the soil and endemicity. A maximal iodine content is found in chernozem soils and a minimal, in podzol soils, which is connected with their water regime. At the same time peat soils also have a high iodine content since peat accumulates iodine. But iodine in peat is so firmly bound with its other substances that plants cannot utilise it.

The adsorptive capacity of the soil and its structure affect the iodine content in it, specifically the extent to which iodine is washed away and desalinified. In some places there is an amazing variety of iodine content in nature, which depends on purely local conditions, for example, the presence of iodine-rich mineral springs even in an iodine-poor locality. Thus, in Borzhomi, Georgia, there are springs with a high iodine content, while districts of Svanetia are poor in iodine and have endemic goitre. The quantity of iodine in nature also depends on local climatic geographical conditions which affect the so-called iodine cycle in nature. In this cycle iodine is found in various states, particularly, free iodine and iodine bound with organic and inorganic compounds. Primary mountain rocks are the main source of iodine. Their weathering and washing out results in the accumulation of iodine first in fresh water and then in sea water and, correspondingly, in marine plants and animals and, lastly, in marine sediments which, in their turn, in distant geological epochs were the basis for the formation of primary mountain rocks. Iodine, weathered

from primary mountain rocks and fresh water, together with water vapours, gets into the air and from there returns to the ground with precipitation, i.e., again enters the waters of rivers and lakes, is absorbed by the soil and from there gets into ground plants. Thus, iodine, together with food, finds its way into the organism of man from various sources, namely, from the air, ground plants and animals, from fresh water and sea plants and animals.

An analysis of the general laws governing the distribution of iodine in nature and especially data on the iodine content of subsoil waters in the Ukraine are well represented in the works of P.S. Savchenko. Detailed investigations enabled the author to formulate a number of propositions, which follow from data of the physico-chemical properties of iodine and the natural conditions of the localities determining the distribution of iodine. Many of these propositions refer to the content of iodine depending on the relief of the terrain, the nature of the soil, the type of mountain rock, the hydrogeological conditions and the geostructure, and also the distance of the locality from the sea, direction of the winds and altitude above sea level. Inasmuch as most of Savchenko's conclusions in the main conform to what we said earlier, we shall mention only new data of special interest since they to a certain extent explain the genesis of endemic goitre in districts near the sea and at a relatively low altitude above sea level.

Savchenko maintains that a big water supply (dense river network), high level of subsoil waters and large amount of precipitation (big drainage) determine a low iodine content in the waters and soils. Proximity to the sea and the altitude above sea level are only of secondary importance in such cases.

Savchenko's data on iodine content in ground waters in the Carpathians, Polesye and the Crimea confirmed a number of his propositions, which were approved at a conference on biogeochemical provinces organised by the Academy of Sciences of the U.S.S.R. in 1957. At that con-

ference V. M. Meshchenko, V. I. Alexeyev and E. A. Mezhvinskaya submitted interesting data on the content of iodine, cobalt, fluorine and bromide in the soils, drinking water and foodstuffs in various biogeochemical provinces of Transcarpathia. These data not only proved the role of iodine deficiency in the aetiology of endemic goitre, but also indicated a definite direction in iodine prophylaxis of goitre (by means of iodised salt, special fertilisers, etc.). According to A. P. Vinogradov, the daily balance of iodine consumption by man in a non-goitrous region consists of the following parts: 70 gamma of iodine from plant food, 40 gamma from meat, 5 gamma from the air and 5 gamma from the water—a total of 120 gamma. Plant food, thus, is the main source of iodine. The quantity of consumed iodine is given as 120 gamma. But for non-goitrous regions it is more correct to take the figure of 200 and not 120 gamma.

A comparison of the daily consumption of iodine by the organism and the incidence of goitre in various districts furnishes an interesting picture of inverse proportion, that is, the higher the content of iodine in nature and the quantity consumed by the organism the lower the incidence of goitre, and vice versa. Data on the consumption of iodine in Bordeaux, Paris, Effingen, Utrecht and Berne are generally known. The figures are as follows: Bordeaux, 200 gamma; Paris, 100 gamma; Effingen, 70 gamma; Utrecht, 40 gamma, and Berne, 20 gamma. Thus, as the quantity of iodine consumed decreases the incidence of goitre rises—from total absence of goitre in Bordeaux to 3 per cent in Paris, 50 per cent in Utrecht and 85 per cent in Berne.

Studies of the soil and water are of essential importance for gaining an approximate idea of the content of iodine in nature. Thus, in Effingen mountain rocks contain from 5,400 to 9,300 gamma per kg of weight and the soil, 11,900 gamma. Whereas the incidence of goitre is 1 per cent in Effingen, it is 12.1 per cent in Gornussen where the mountain rock contains 830 gamma of iodine and the soil, 4,940 gamma of iodine. In Gunsenshville the incidence

of goitre rises to 56.2 per cent; here the content of iodine per kg of mountain rock ranges from 320 to 700 gamma and in the soil it is only 620 gamma.

Numerous studies of the iodine content of water show that in goitrogenous regions the quantity of iodine in the soil drops and at times can be measured only with difficulty. It was established that the waters, particularly subsoil waters, reflect in sufficient measure the content of iodine in nature in the given locality. For example, Fishler points out that in most endemic goitre areas in the vicinity of Danzig drinking water contains only 2.5 gamma of iodine per litre on the average. In districts of low endemicity the quantity of iodine rises and in non-goitrous areas reaches 30 gamma and higher per litre. To what extent the iodine content in the water of rivers, lakes and other sources is an index to the content of iodine in rocks and soils of the basins drained by these sources, and to what degree this iodine content reflects on the incidence of goitre is shown by data for some places in the states of Michigan and Ohio in the United States. In four of these places the iodine content in the water was as follows: 0, 0.5, 7.3 and 8.7 gamma per litre; the incidence of goitre dropped correspondingly from 64.4, 56.6 and 32.7 to 26 per cent in the last place.

Numerous investigations made by Soviet authors, including researchers of the Institute of Geochemistry and Analytical Chemistry, U.S.S.R. Academy of Sciences, have invariably established the coincidence of endemic goitre areas and zones with iodine deficiency in nature. It is interesting to note that under certain, at times considerable, fluctuations of the iodine content in nature, man becomes accustomed to a very definite level of iodine consumption in the given locality (Vinogradov). The studies made have revealed a lower iodine content in water of goitrogenous regions. All these investigations have established a dependence between the iodine content in water and the incidence of goitre among the consumers of this water, with a

higher endemicity usually conforming to a lower iodine content in the water. It is interesting that when studying the water in Yaroslavl Region (investigations of V. A. Florinsky under the guidance of V. S. Chetverikov), a low iodine content was revealed. At the same time these studies brought to light iodine-rich waters in bored wells with a content of up to 64 gamma of iodine per litre, the use of which can protect the population from goitre.

A parallel study of the iodine in the blood and thyroid tissue, measurements of the daily ingestion of iodine with the food and its excretion in the urine make it possible to establish with high precision the daily iodine ration and the state of iodine metabolism in man. The form in which the iodine gets into the organism essentially affects its absorption. In determining the daily ration, account should be taken of iodine losses in preparing the food (V. M. Meshchenko and others). Latest physiological data, obtained by using iodine isotopes, also corroborate the importance of iodine deficiency in the aetiology of endemic goitre and in the origin of iodine starvation. Thus, a study of I^{131} uptake by the thyroid of healthy people in endemic goitre districts of Khakassia in conditions of iodine deficiency revealed a noticeable increase in the absorption of iodine by the thyroid and its accumulation in the gland. This higher uptake of iodine depends not on hyperthyroidism or thyrotoxicosis, but only on iodine starvation, that is, the iodine deficiency in the organism and in the thyroid. Consequently, in evaluating the degree of uptake of radioiodine and the function of the thyroid in an endemic goitre area it is necessary to reckon with the degree of iodine deficiency in nature, in the food ration and with the compensatory potentialities of the organism.

Numerous data on the iodine content in the environment, examined in the light of the problem of trace elements and the unity of the organism and the environment, acquired special significance in connection with the physiological data on the role of iodine in the organism and, specifically,

the physiology of the thyroid. The thyroid which produces the iodine-containing hormone, thyroxin, is naturally the main concentrator of iodine needed for the synthesis of this highly important hormone required by all the tissues of the organism, the nervous system included.

The most important metabolic processes take place only when thyroxin is available and any partial removal of the thyroid in experiments invariably causes a corresponding compensatory reaction. As early as 1896, Holstead demonstrated that removal of a greater part of the thyroid induces in the remaining part phenomena of hyperplasia, which in essence is a compensatory reaction process. Phenomena of hyperplasia were subsequently found by Marine in the thyroid of domestic animals and man in endemic goitre areas. Chemical investigations have established that the greater the enlargement of the thyroid the smaller the concentration of iodine in it. When Holstead's experiment was duplicated and extended, it was established that hyperplasia of the remaining part of the thyroid does not set in if, following subtotal thyroidectomy, a surplus of iodine is artificially introduced. When hyperplasia already sets in the excessive influx of iodine causes a normalisation of the function in the remaining part of the thyroid, although its follicles remain distended, resembling the picture of a colloid goitre.

When the influx of iodine into the organism was repeatedly reduced, alterations took place in the remaining part of the thyroid accompanied by processes of hyperplasia and fibrous atrophy characteristic of destructive processes in endemic goitre. Harington who studied in detail the chemistry of the thyroid hormone, thyroxin, rightly maintains that even a mere comparison of the results of experimental investigations with data on the nature of the thyroid hormone and the latter's function leads to the only correct biochemical explanation of the aetiology of endemic or, as he calls it, simple goitre, on the basis of the significance of iodine deficiency in nature.

The above data do not exhaust the materials which demonstrate the internal connection of changes in the iodine balance of the organism with iodine deficiency of the biosphere as seen in definite geochemical manifestations. But even these materials are sufficient for arriving at the conclusion that the iodine deficiency theory in the aetiology of endemic goitre has fully justified itself.

Many factors influence the consumption of iodine by the organism. Hence there is no full parallel between the degree of iodine deficiency in nature and the degree of goitre endemicity. The form of the iodine compounds also affects the assimilation of iodine by the organism and its excretion in the urine. According to Fellenberg, iodine contained in cod liver oil assimilates excellently, iodine of plant and animal origin assimilates well, but the assimilation of mineral iodine is poorer. Experiments conducted by Seel in 1954 confirmed that biological compounds of iodine are assimilated by the organism more intensively than its inorganic compounds. There is no doubt that as the daily influx of iodine into the organism declines, as compared with the optimal, man's organism as a whole responds with changes in the processes of iodine metabolism and the function of the thyroid which accumulates and synthesises the iodine into the hormone. The numerous factors and conditions that act on the organism as a whole, the neuroendocrinal system, the system of ferments and electrolytes influence the use of iodine by the thyroid, its size, structure and function. But, as pointed out earlier, under certain favourable conditions the insufficient influx of iodine into the organism might not cause alterations of the basal metabolic processes in view of the adaptation of the organism and the compensation of the inadequate influx of iodine.

In summing up, it should be said that iodine deficiency in definite geographical areas and the attendant alterations of iodine metabolism in the organism and the synthesis of the thyroxin hormone should be regarded as the leading

aetiological factor which determines the most essential phase in the pathogenesis of endemic goitre, namely, the phase of specific goitrous endemic hyperplasia of the thyroid.

The social and living conditions, sex, age, non-specific intoxication of various origin and irrational diet are, as pointed out earlier, additional factors of essential significance in the aetiology of endemic goitre. It is against this background that endemic goitre develops. The above-mentioned endogenic and exogenic conditions play an important part in realising the action of iodine deficiency as the causal factor which determines the development of the disease; these conditions turn the possibility of endemic goitre into reality.

Clinical Picture

The clinical picture of pronounced forms of endemic goitre is strikingly delineated and its characteristic presents no particular difficulty. It is somewhat more difficult to delimit the boundaries between the normal physiological adaptational reaction of the organism, which fully compensates for the insufficient influx of iodine, and the beginning of endemic goitre when the physiological measure of protection (Pavlov) is inadequate.

There is no doubt that a nodular goitre is an unconditional symptom of the disease in a pronounced form. As for the diffuse enlargement of the thyroid, the nature of this enlargement can be reliably established only by a thorough clinical study of the patient, taking into account data of the dynamic examination of the population. In the course of such an examination it is revealed that in the case of persons in the pubescent period a diffuse thyroid enlargement of the I, II and at times even III degree, far from progressing, disappears completely in time. In this case it may be confidently said that such an enlargement of the gland was not an initial symptom of the disease. In such cases it

may be assumed that the insufficient influx of iodine into the organism increases the endogenous deficiency of iodine connected with the greater need for the thyroid hormone by the organism in different conditions—physiological (menstrual cycles, pregnancy, sexual maturing) and pathological (various diseases, especially infectious, and also physical and emotional stresses of various kinds).

In other cases in goitrogenous regions thyroid enlargement at some period becomes already the beginning of endemic goitre. For practical purposes in mass examinations of the population, it has been agreed to differentiate between thyroid enlargements of the I and II degrees, on the one hand, and III, IV and V degrees, on the other. Only the latter degrees of thyroid enlargement are called a goitre in the Soviet Union, while in a number of other countries any thyroid enlargement is designated as a goitre or initial stage of goitre. There can be different solutions of this question and objective tests should be sought for correctly determining the beginning of pathology. Lately data have been made public, particularly by Spanish authors (G. Escobar, F. Escobar and del Ray, we are quoting Stanbary), indicating that in some of the patients with goitre a definite fraction of the iodine compound can be obtained from the blood serum, the nature of which is not known so far, but its chemical structure differs from thyroxin and triiodotyronine. This speaks of a qualitative alteration in thyroid function not only in hypothyroid cretins, but in euthyroid goitre as well.

Definite data in this respect are being accumulated. The term "large thyroid", introduced by Hunzieker, stresses that in goitrogenous regions the diffuse enlargement of the thyroid and the general elevation of its weight curve are regarded as a manifestation only of the physiological compensatory reaction of the organism, i.e., a thyroid enlargement is by no means always a sign of disease. At first this enlargement represents an easily reversible process. But such a thyroid enlargement which has no pathological

importance for one geographical area might already be a pathology in another area. Here we do not speak of pathological alterations in the thyroid when a pronounced disturbance of its function is in evidence. In each separate case of thyroid enlargement it is necessary to be guided by a careful study of the patient's anamnesis, local and general symptoms and the presence of symptoms of goitre development. In such instances the most proper method for determining the pathologic importance of thyroid enlargement is to take into account the conditions in the goitrogenous region.

Very often in goitrogenous regions a mild degree of diffuse thyroid enlargement, if it is not accompanied by an alteration of the gland's function, has no pathological significance, but speaks of iodine deficiency in nature. In these cases definite prophylactic measures are needed since even such an enlargement of the thyroid attests to the insufficient influx of iodine into the organism.

As pointed out earlier, three main forms of goitre are differentiated: diffuse, nodular and mixed. In diffuse enlargement of the thyroid the latter is evenly hyperplastic in all parts and, by palpation, it is impossible to establish the formation of nodules which constitute an adenomatous hyperplasia. But in endemic diffuse goitre the presence of small adenomas is not precluded and they are not as rare as, for example, in other thyroid diseases. A diffuse goitre is always two-sided and usually its localisation conforms to the normal position of the thyroid. The variants of diffuse goitre localisation differ little and in this respect offer a contrast to nodular goitre which is subordinated to the law of blastomatous growth. In nodular adenomatous goitre a more or less substantial part of the thyroid might remain absolutely normal or can be only slightly hyperplastic. In this normal or slightly altered thyroid tissue a single or multiple nodules or adenomas are formed, which are encased in a fibrous capsule and are clinically defined as a neoplasm. The thyroid tissue around the nodule might be

subjected to considerable atrophy. A nodular goitre can be both one-sided or two-sided, its size and consistency vary, with the uneven nature of the nodules in multiple conglomerate goitre making it easier to identify it clinically.

Among patients with endemic goitre those with the nodular type constitute the main contingent that get into surgical wards. In mixed forms of goitre small nodules are seen against the background of the diffusely hyperplastic thyroid. It should be noted that, on the one hand, a dense diffuse goitre, particularly when the borders of the pyramidal lobe or the enlarged isthmus distinctly stand out, at times creates the false impression of the presence of nodules, while, on the other hand, when examining a one-sided, soft nodular goitre, it is mistaken for a diffuse goitre. If the goitre (III and IV degrees) is one-sided and on the opposite side a normal or slightly enlarged thyroid lobe is palpable, it is almost always possible to assert that it is a nodular goitre. Correct diagnosis in such indistinct cases is of great importance for the timely prescription of the proper therapy, since the latter differs in principle in diffuse and nodular endemic goitre.

Endemic goitre is also differentiated by the functional state of the thyroid and the organism. There are euthyroid, hyperthyroid and hypothyroid goitres.

Euthyroid goitre is not accompanied by any noticeably pronounced alterations of the thyroid function. Patients with euthyroid goitre make no special complaints characteristic of the hypo- or hyperfunction of the thyroid. Hyperthyroid and hypothyroid goitre are determined by the symptoms inherent in each.

Undoubtedly, in all cases of pathological alterations in the thyroid there are not only quantitative but also qualitative changes in its functions, which has been proved by some investigations made in recent years. This has given some authors grounds for speaking of endemic goitre as a goitrous endemic disease. But the term "endemic goitre", too, presupposes a disease of the entire organism, and not

a local process. The term "goitre" without "endemic" indeed defines only a local sign of thyroid enlargement which has the nature of a pronounced swelling in the region of the neck changing its configuration.

Among the hyperthyroid forms of goitre so-called thyrotoxic adenomas are singled out. Thyrotoxic nodular goitre is relatively more frequent in places of low goitrous endemicity or along their borders in areas with an endemic thyroid enlargement where diffuse forms prevail. In areas of high endemicity nodular goitre is more frequently accompanied by hypothyroidism. Nodular goitres, as a rule, are sporadic goitres, which does not refute the facts, firmly established by various authors, concerning the undoubted influence of the degree of endemicity on the frequency of nodular forms. This has been well demonstrated by the materials of our expedition in the Zeravshan River valley of Uzbekistan. Deviations in the development of the thyroid, differences in the configuration of the neck and the formation of goitre determine the diversity of its localisation, in view of which some forms have been specially designated. For example, circular, intrathoracic and hanging goitre are differentiated. The intrathoracic form is subdivided into full and partial, diving and wandering. A goitre can be posterior tracheal, laryngeal, supra-laryngeal and lingual. Of special interest is the lingual goitre which develops from elements of the thyroid, from the rudiment of the embryonal thyroglossal duct preserved at the basis of the tongue under its mucosa.

An aberrant goitre develops from additional lobules of the thyroid in the lateral parts of the neck. It is especially susceptible, like any ectopic tissue, to malignant degeneration. Such an aberrant goitre can be singular or multiple. Among the nodular forms there is a special one, the so-called metastasising adenoma. Histologically it is characterised only by somewhat elevated proliferative phenomena, at times the papillomatous proliferation of the epithelium, but it has no morphologically determined signs of malig-

nancy. The proliferated epithelium has no infiltrating growth and even the metastases in far removed parts of the organism, most often in the bone, have a histological structure of a normal thyroid.

It should be noted that the diagnosis of different nodular forms of goitre should be made without resorting to punctates or biopsy. When in doubt in cases suspected of malignant degeneration, it is better to resort to radical surgical intervention without a sufficiently precise diagnosis. Of late radioiodine diagnostics has been used as an aid in complicated cases.

The size of the goitre varies greatly and is determined by the scale given earlier of the degree of thyroid enlargement. Owing to the successful drive on endemic goitre very large goitres are rare now, but some 20-30 years ago goitres weighing up to 2 or 3 kilograms could be seen (Fig. 30). The size of the goitre can be measured with a tape, determining the lateral and longitudinal diameter of the goitre. It is somewhat more difficult to determine the thickness of the goitre.

Fig. 30. A very large multinodular goitre.

The consistency of the goitre can be even or uneven, a goitre might be soft, dense, moderately dense, tensely elastic and hard. It can be mobile, partly mobile

or immobile with regard to the underlying tissues. The difference in consistency, lobulation and uneven growth of separate parts of the nodular goitre diversify its configuration, which often sharply alters the normal topographical proportions in the region of the neck. At times bruits can be heard when auscultating the goitre.

The diversity of forms of goitre, its localisation, size and topographical conditions, which change in connection with its development, explain the diversity of symptoms of mechanical irritation of the tissues surrounding the goitre and goitre compression on the neck vessels, organs and tissues. As a rule, in small diffuse thyroid enlargements and in the absence of particular functional alterations both in single and multiple nodules which do not grow substantially, patients make no complaints. At times only cosmetic considerations bring the patient to the doctor. Most patients with endemic goitre do not complain of their disease or speak only of a small inconvenience in the region of the neck, which increases during work, when buttoning the collar or at night during sleep when the patients wake up because the goitre presses on the trachea. Most often such patients do not complain at all and they do not associate the disturbances in the organism with the goitre. At times patients complain of difficulty in breathing, more seldom of a change in voice or huskiness, fits of asphyxia. Very seldom patients notice difficulty in swallowing; disturbance of blood circulation in the region of the neck and head is observed frequently. This is expressed in a feeling of unpleasant corpulence, stress in the head, especially when bending; distention of the subcutaneous cervical veins is noticed owing to the difficulty in the flow of blood from the jugular veins. These disturbances in blood circulation with the formation of distended venous collaterals are especially pronounced in intrathoracic goitre which is wedged in the upper opening of the thorax.

Disturbances of blood circulation, connected with the

simultaneous alteration of respiration, extend to the small blood circle and lead to hypertrophy and dilatation of the right heart. In pronounced thyroid intoxication these changes of a mechanical order cause a so-called "goitrous heart". Hence complaints of such patients of heaviness and short wind. This can weaken cardiac activity and disturb blood circulation in the big circle. The distended veins on the anterior surface of the thorax in intrathoracic goitre acquire the shape of *caput medusae*. The symptom of irritation or inhibition of the trunks of the sympathetic and other nerves is often seen.

But the general changes in euthyroid endemic goitre are so insignificant that they cannot be compared with the general symptoms of primary thyrotoxicosis (Basedow's disease), when the goitre as a symptom is not pronounced against the background of the general pathological alterations. The course of the pathological process in endemic goitre is affected by the same factors which promoted the onset of the disease and were described in the aetiology of endemic goitre. The slow development of the goitre can give way to a sudden acceleration of its growth during pregnancy or after an abortion or, lastly, after a psychic trauma when symptoms of secondary thyrotoxicosis arise. Complaints of the patients and anamnestic data, when compared with data of an objective clinical study, acquire particular importance in determining the nature of the goitre. Thyrotoxic phenomena are usually moderately pronounced and do not become as intensive as in a real Basedow's disease. They are seen most often in young patients, particularly women, in toxic adenomas or primary thyrotoxic nodular goitres. At times such hyperthyroid goitres occur in goitrogenous regions as a sharply developing mass disease ("goitre epidemic") or are seen in visitors who come to goitrogenous areas from non-goitrous districts. Even in places where the endemicity is characterised by frequent cases of hypothyroid forms of endemic

goitre, the goitre arising in visitors often has symptoms of hyperthyroidism.

Similar hyperthyroidism, which develops in patients with goitre in goitrogenous regions, is often seen after excessive ingestion of iodine, particularly so-called microdoses, which in reality greatly exceed the organism's requirements in iodine. In most high endemicity areas with a substantial percentage of this disease a change from the euthyroid state of a patient to hypothyroidism is observed, and in cases of families sick with goitre from generation to generation endemic cretinism develops. Very frequently, even in patients who make no complaints and whose goitre is qualified as euthyroid, during mass examinations a careful investigation reveals elements of hypothyroidism. This is particularly true of areas where iodine prophylaxis or iodine therapy have so far not been applied.

In pronounced cases of hypothyroid goitre the influence on psychic and physical development is very striking. The general appearance of the patient, his puffy face, characteristic pale and dry skin with changes in subcutaneous cellular tissue, general sluggishness of vital processes, inclination to constipation, poor growth of hair and other hypothyroid symptoms, make it possible to speak of pronounced hypothyroidism in endemic goitre; in a number of cases features of endemic cretinism too can be noticed in such patients (Fig. 31, 32). M. Y. Breitman rightly emphasises that cretinism is associated with deep pathology which begins in the embryonal period or in early childhood. Cretinism has never been observed in people who come to an endemic goitre area, because their thyroid had developed normally before they came to that region. Cretinism is inborn, and in goitrogenous regions there are cretinoids or patients with separate features of cretinism. A cretin, according to de Quervain, differs from people with thyroid aplasia first of all in that his thyroid is in a state of acute goitrous degeneration. Distortion of the function of such a

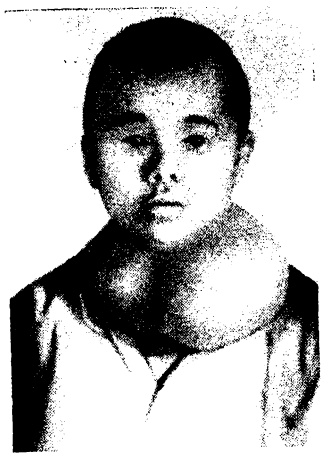

Fig. 31. A cretin woman, 22 years old.

Fig. 32. Same patient two months after the operation.

gland is accompanied by deep alterations in various organs and systems. The appearance of cretins is very characteristic. They are clumsy in their movements and weak, often inadequately react to outside irritants, not infrequently smile for no reason at all. General retardation of growth with disproportional development of separate parts of the body, especially the extremities, is combined with a sharp retardation of psychic development. The structure of the facial part of the cranium with the sunken bridge of the nose and a number of other features, specifically, dry and puckered skin of the face, together with its puffiness and paleness, poor growth of hair—such are the characteristic features of a cretin. Their muscles are unevenly developed and flabby. Acute psychic backwardness, frequent tongue-tie and deaf-muteness make the cretins in most cases unsuitable even for the most elementary work. Endemic cretinism is found most often in goitrogenous regions with bad social and living conditions and poor sanitary-hygienic conditions.

Endemic cretinism should not be confused with chondro-

dystrophy, pituitary dwarfism, idiocy with slanty eyes (Langdon-Down disease), sporadic idiopathy and other similar conditions.

In areas of high endemicity where cretinism is observed, there is, as a rule, great incidence of goitre among animals. Even in such goitrogenous regions the goitre of most patients is predominantly of a euthyroid character with a disposition towards hypothyroid phenomena in a number of cases. Study of the basal metabolism in patients with endemic goitre, as a rule, reveals normal values, more seldom fluctuations within a range of —20 up to +30. Evidently in hypothyroid phenomena the basal metabolism is usually decreased in cretins as well. It is interesting that special investigations of thyroid radioiodine uptake among the population in endemic goitre areas shows that iodine is intensively absorbed by the thyroid of normal people who have no goitre and also of those who have an enlarged thyroid of the I, II and III degrees, if the thyroid has not been subjected to destructive processes. This elevated absorption of radioiodine is a result of the iodine starvation of the organism, owing to which iodine is actively taken up by the thyroid and is kept longer than normal. This elevated absorption of iodine by no means attests to the presence of a clinical picture of hyperthyroidism. In most cases there is an obvious non-conformity between the clinical data and the results of radioiodine investigations. Moreover, this non-conformity also extends to data of the basal metabolism which, alongside higher values of radioiodine uptake, can be normal or even lower in patients with nodular goitre and sharply pronounced changes in the thyroid tissue. This applies particularly to patients with cretinism. Radioiodine is poorly absorbed by the thyroid of cretins, which points to the inability of the thyroid to synthesise the normal hormone, thyroxin. The considerably reduced biological activity of the tissue, of the goitrously altered thyroid can be judged from studies which use the methods of Hudernatch, i.e., observation of

the metamorphosis of tadpoles under the influence of goitre tissue removed during operations.

In clinical studies of patients with endemic goitre laboratory data usually do not deviate from the norm, although some authors studying the blood of patients found eosinophilia which reaches high figures. But often it is very hard to judge the causes of eosinophilia, especially in places with widespread helminthism. At times in patients with endemic goitre the leucocytic picture shifts to the left, and there are atypical monocytes, Turk's irritation cells, degenerative neutrophils, polymorphism of the platelets and a higher number of reticulocytes (S. I. Sherman). A special investigation of oxidative-reduction processes (M. N. Tumanovsky) in the changed function of the goitrously degenerated thyroid revealed a definite shift in the correlation of the fraction of glutathione and an alteration of the oxidative-reduction processes in the blood. The iodine content in the blood of patients with endemic goitre, as a rule, is somewhat lower as compared with normal values, which range from 8.3 gamma of iodine in winter to 12.8 gamma in summer in 100 g of blood (Weil and Sturm).

The latest methods of studying the function of the thyroid with the aid of radioiodine make it possible to establish the difference in the absorption of this isotope by a goitrously altered thyroid, normal tissue, hyperplastic tissue or separate nodules of the gland. In some cases a sharp elevation of radioiodine uptake by a nodule in the thyrotoxic adenoma, while the absorption of iodine by the surrounding thyroid tissue is normal, is of great practical significance in choosing the method of surgical intervention. In this case the scope of surgical intervention is being decided, namely, whether to remove the adenoma only, i.e., enucleation, or to resect the entire thyroid, which is of great importance for postoperative prognosis.

Differential diagnosis of endemic goitre with primary thyrotoxicosis (Basedow's disease), as a rule, presents no difficulties. For this it is sufficient to establish the place

of birth and permanent residence of the patient, when the disease began and its nature at that time, its symptomatology and course. But in cases when the patient had an endemic goitre for many years and thyrotoxicosis developed under the influence of a psychic trauma, the question often arises whether it is a new disease developing against the background of endemic goitre or the endemic goitre itself is Basedowificated, that is, alterations in the hormonal activity of the goitrously changed tissue have occurred.

It is also necessary to differentiate endemic goitre from chronic non-specific thyroiditis of the type of the lymphomatous Hashimoto's struma and so-called iron-like fibroplastic Riedel's struma (see Chapter IV), which frequently resemble a malignant goitre. Thyroiditis, as a rule, covers diffusely the entire gland and frequently is accompanied by hypothyroidism. At times it is difficult to differentiate an intrathoracic goitre from a tumour of the mediastinum and a dermoid cyst. The use of a radioiodine test helps in the diagnosis. When the goitre is of a cystous nature it is necessary to differentiate it from lateral neck cysts which usually do not shift when swallowing, in contrast to a goitre which follows the movement of the trachea.

In differential diagnosis it is important to bear in mind goitre of the carotid gland and adenoma of the parathyroid glands observed in hyperparathyroid osteodystrophy and also tumours of the lymph nodes, nerves and other neck tissues.

Among the main complications in the development of goitre are haemorrhages into the tissue of the goitre, inflammation or strumitis and malignant degeneration of the goitre. If haemorrhage takes place into the cavity of a large cyst, owing to the sudden increase of its size, there arise at times acute phenomena of stenosis of the trachea. A small haemorrhage passes unnoticed or is accompanied by a mild sensation of pain and stress in the goitre. Usual-

ly a haemorrhage leads to destructive aseptic necrobiotic processes in the goitre. This might ultimately lead to puckering and decrease in size of the cicatricising goitre. Inflammatory processes might reach various stages of development up to suppuration.

Inflammatory phenomena determine the development of corresponding changes: the goitre becomes almost immobile, its consistency changes and the function of the thyroid is often disturbed. At first inflammatory phenomena are frequently accompanied by symptoms of hyperthyroidism; when the inflammatory phenomena are removed hypothyroidism might set in. At times, as a result of an inflammation process in the solitary nodule of a goitre, the nodule disintegrates and cicatricises, leading to the selfcure of the goitre. Suppurative strumitis is very rare. At times it opens up into the region of the neck, forming fistulas which do not heal. The walls of such struma might be calcinified. We have seen fistulas after strumitis which were many years old and were supported by ossified sections of the goitre which played a part similar to sequestra in osteomyelitis.

Malignant degeneration of goitre is seen much more frequently. In the initial period it is very difficult to determine it not only by clinical data, but even by histological study of a resected goitre. Cancer frequently comes as a sudden pathohistological discovery. One of the characteristic signs of malignisation of a goitre is its intensive growth in one section of the nodule or resumption and intensive growth of the goitre in stationary forms of nodular goitre. In such cases the goitre becomes mobile only in part, the voice of the patient changes at times and irradiating pains appear in the region innervated by the cutaneous nerves, behind the ears. Signs of malignant degeneration become absolutely clear in very advanced cases of cancerous degeneration when metastases in the neck lymph nodes appear. At times it is difficult to decide whether these are metastases or an aberrant goitre, i.e., a goitre which grew

from ectopic ordinary thyroid tissue. We fully agree with N. N. Petrov who proposes that each case of nodular goitre in people of middle age and older be regarded as a pre-cancer state. Each patient with nodular goitre, especially if signs of growth of this goitre are in evidence, should be placed under the observation of a surgeon. In fact, every case of nodular goitre demands caution on the part of the doctor. Conservative treatment, as a rule, is unsuccessful in such patients, except early cases of conglomerate goitre when thyroidin might produce a favourable effect. But this medication is possible only in euthyroid and hypothyroid goitre without destructive changes.

There are no exact data as to the frequency of malignant goitre degeneration. In any case in patients who have a goitre for a long time the danger of cancerous degeneration sharply rises with age. It is much greater in goitrogenous regions than in non-goitrous areas. It is known from data in literature that cancer of the thyroid occurs 20 to 30 times more frequently in goitrogenous regions than in non-goitrous areas.

Diagnostic difficulties also frequently arise when the adenoma metastasises without any noticeable growth of the goitre itself. In such a case the use of radioiodine can help to diagnose metastases of cancer or metastasising adenomas in distant organs (these metastases occur frequently in the lymph nodes and in the bone system). Studies with the aid of tracer doses of radioiodine help to determine the uptake of radioiodine in the metastases of cancer of the thyroid or a metastasising adenoma, which in essence behaves like a malignant neoplasm, although histologically the structure of these tumours often does not give a picture of a malignant neoplasm. It should be noted that the great frequency of malignant degeneration of the thyroid in goitrogenous regions tallies with experimental data, showing that neoplasms transplanted to the test animals grow better against the background of iodine deficiency.

There are experimental data showing that thiourea can also promote the malignant degeneration of the thyroid. The same takes place when the thyrotropic hormone is administered to animals for a long time. Experimental malignant neoplasms of the thyroid were induced under its influence without the additional action of any other cancerigenic factors. The experimental reproduction of such neoplasms was observed in rats when radioiodine was used. It is interesting that the malignant neoplasms were formed only 1.5-2 years after a single administration of radioiodine. At times in cancer of the thyroid hyperfunction of the non-affected parenchyma of the thyroid surrounding the neoplasm was observed. But the uptake of radioiodine by the cancer tissue drops sharply. Besides cancer, the malignant neoplasms of the thyroid include sarcoma, hemangio-endothelioma and some other neoplasms.

In conclusion it should be noted that endemic goitre in various geographic areas has its distinctions both of a functional and morphological nature.

By studying the anamnesis of the patient, paying attention to his permanent residence or temporary stay in goitrogenous regions and knowing the degree of endemicity, a doctor is able to diagnose endemic goitre, correctly differentiating it from various other diseases accompanied by similar symptoms of thyroid enlargement. Knowledge of the clinical picture of endemic goitre in various regions and of the environment in these regions, in the broadest sense of the word, enables doctors to apply most correctly individual treatment and to use the most effective antigoitre remedies.

Prophylaxis and Treatment

The above data on endemic goitre and knowledge of the laws of its development dictate a definite policy in its prophylaxis and treatment. General health measures—an

improvement of the sanitary living conditions and the sanitary-hygienic situation—are needed above all for the prevention of this disease. By taking into account the local conditions and proposing improvements most important for the given area, particularly the building of a water works and sewerage system, development of fruit and vegetable growing to improve the diet of the population, by conducting hygienic propaganda, it is possible sharply to reduce the incidence of goitre. Greater water consumption per capita is a powerful anti-goitre health factor even in cases when the water remains deficient as regards its iodine content. More healthful working and living conditions of the population in goitrogenous districts provide an important background for the success of iodine prophylaxis of goitre and its treatment.

Iodine prophylaxis of endemic goitre has always been closely associated with iodine treatment. Indeed, each case of treatment of endemic goitre, if it is aetiologically and pathogenically justified, should yield a positive result. The use of iodine, if the treatment is prescribed in the early stages of goitre development, prevents its further growth. The two main forms of mass iodation of the population in goitrogenous regions, namely, the consumption of so-called full-value iodised salt and the mass prophylactic iodation of children beginning at an early age, especially in school, should be regarded as real prophylaxis of goitre.

We know from the history of medicine in China and other countries that long before the presence of iodine in various types of sea sponges, sea cabbage or in edible algae was established, the latter had been consumed with the object of preventing and treating endemic goitre. But it was only after the studies of Prevost and Chatin that iodine prophylaxis began to acquire a scientific foundation; at the beginning, this prophylaxis involved dangers from the introduction of excessively large doses of iodine into the organism and only subsequently, when data on the daily iodine requirement of the organism were established

more precisely, did iodine prophylaxis acquire physiological substantiation.

In 1919, Bajard for the first time ascertained the minimal quantity of iodine which has a prophylactic and curative effect in goitrogenous regions when administered to school children. In 1922, the Swiss Goitre Commission advocated, with full grounds, the wide prophylactic use of iodised or full-value salt with a content of from 5 to 10 g of potassium iodide per ton. In some localities natural salt contains iodine in quantities exceeding those indicated by Bajard as having a prophylactic effect. In 1919, Bajard used with success iodised salt containing 0.02 g of potassium iodide per 5 kg of salt.

The wide use of iodised salt in the Soviet Union began after the success of the experiment, arranged on the initiative of O. V. Nikolyaev, of using iodised salt in the Kabardino-Balkarian Republic in 1933. The experiment in iodine prophylaxis of goitre, conducted among the population of a whole republic, at first produced a sharp reduction and then the complete elimination of the incidence of endemic goitre. At that time iodised salt containing 7.5 and then 10 g of potassium iodide per ton of salt was used. At first this iodised salt was prepared locally by semi-handicraft methods, but subsequently a factory method of iodising salt was developed. Iodised salt containing 25 g of potassium iodide per ton of table salt is now used in the Soviet Union. The use of such full-value salt ensures the daily requirement of iodine. In localities where iodine prophylaxis has been conducted properly for years, the number of patients with endemic goitre has been sharply declining; there are no cases of goitre among new-born infants, and the number of operations for goitre has been greatly reduced (Fig. 33).

In addition to Kabardino-Balkaria, goitre as a mass disease has been fully stamped out in a number of other regions and areas of the Soviet Union. Particularly great successes have been registered in Azerbaijan, the Urals,

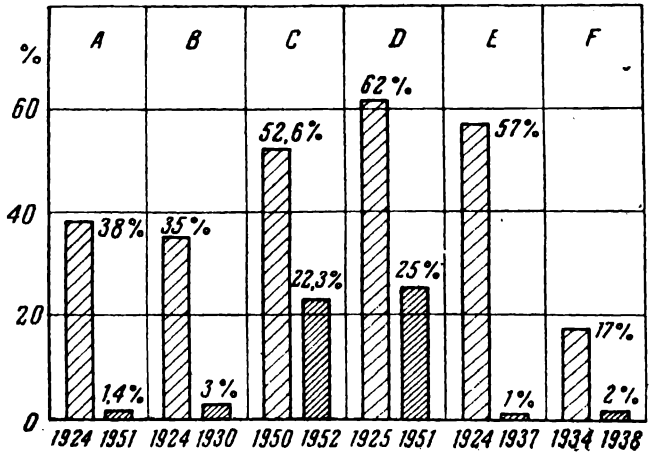

Fig. 33. Decrease in number of goitre cases as a result of the use of iodised salt, according to data of Holman

Lighter shaded columns—before introduction of iodised salt; heavier shaded columns—after introduction of iodised salt. *A*—State of Michigan, U.S.A.; *B*—Detroit, Michigan, U.S.A.; *C*—North Caldas, Colombia; *D*—Christchurch area, New Zealand; *E*—Lausanne, Switzerland; *F*—Cracow Region, Poland.

Georgia, Western Ukraine, Byelorussia and other areas known in the past as regions of pronounced endemicity. Iodine prophylaxis is now the generally recognised specific and chief method of combating endemic goitre. Its efficiency depends on the level of organisation of this work and the conditions in which it is carried out.

Sanitary control over the production of iodised salt, its proper packaging, transportation and storage in suitable conditions to prevent the loss of iodine from the salt, is exceedingly important. The standard iodine content of salt is not the same in different countries. While in the Soviet Union salt of full value contains iodine in a concentration of 1:40,000, in Poland the required concentration is 1:200,000; in Britain, Switzerland, the Netherlands, Italy and Yugoslavia, 1:1,000,000; in Mexico, Argentina and other countries, 1:60,000-1:30,000; in New Zealand, 1:20,000; and in Canada and the United States, 1:10,000.

The Latin American conference on nutrition problems, held in Venezuela in 1953, arrived at the conclusion that the content of potassium iodide must be not less than 1:20,000 and not more than 1:10,000. But a number of authors, specifically D. Marine, holds, and the experience of Switzerland demonstrates, that the use of salt with an iodine content of 1:100,000 is fully effective.

What are the criteria of the need for endemic goitre prophylaxis and what percentage of children with signs of thyroid enlargement during the period of sexual maturity can be considered normal? P. Stocks regards as normal a situation when only 1 per cent of the boys and 4 per cent of the girls at the age of 12 have an enlarged thyroid. M. Murray and his co-workers regard as normal thyroid enlargement among 6 per cent of school children between the ages of 11 and 15. Matovinović and Ramalingaswami think that when the proportion is higher than 10 per cent iodine prophylaxis is needed. We believe that iodine prophylaxis is required not only in pronounced goitrogenous regions, but also in all biogeochemical provinces with iodine deficiency in nature. This also applies to areas of small endemicity and to nearby districts. The efficacy of iodine prophylaxis is greatly enhanced by general health measures improving the sanitary-hygienic conditions and by an advance in the material and cultural standards of the population. Experience shows that in using iodised salt account should be taken of the distance from the factories producing this salt to the goitrogenous regions. In some countries where salt has to be transported to distant areas simple semi-factory equipment is used for iodising the salt directly in the goitrogenous regions. The use of such local methods merits attention and has fully justified itself in many areas.

A number of factors influences the iodine standard of the salt. Knowledge of these factors is essential for raising the efficacy of iodine prophylaxis. The preparation of iodised salt in places of consumption makes it possible to

vary the standard, depending on the iodine deficiency in nature in the given environment and the level of the daily iodine ration. The question has also been raised of iodising not only salt but also various foods, for example, bread and tea, in places where the population owing to local conditions does not use the iodised salt on sale. The question is also being studied of iodising the soil with the aid of iodine-containing fertilisers.

Data on the results of iodine prophylaxis in Switzerland are of interest. Particularly convincing in this respect are the figures given by Kelly and Snedden. They refer to the frequency of pronounced forms of goitre per 1,000 men examined when called up for military service. The data are given in round figures. Prior to the introduction of iodine prophylaxis in Switzerland, in 1900 there were 93 patients with endemic goitre and in 1905, 116; in 1921, a year after iodine prophylaxis had been started, this figure declined to 55; in 1925 it was 30; in 1935, 11; in 1939-1949, 1.5 and in 1945, 0.6 per 1,000. In 1947, only 7 people with an enlarged thyroid or with goitre were found per 10,000 men examined.

The feeding of iodised salt to farm animals is of great importance in the campaign against endemic goitre. It exerts a favourable influence both on the animals and on man by raising the iodine content of milk and meat consumed by the population.

So-called group or school prophylaxis is of special importance. It consists in the weekly ingestion of 1 mg of potassium iodide which is contained in special tablets manufactured in the Soviet Union and called Antistrumin.

In 1931, having started for the first time in the Soviet Union mass iodine prophylaxis, we worked out methods of group prophylaxis by iodising food. Once a week the necessary solution of potassium iodide, calculated on the basis of 1 mg potassium iodide per person, is added to the food (soup pot, or the like). Some deviations in the dosage are of no essential significance. This experience was then

utilised by a number of authors (M. N. Akhutin in 1933-1934 and others) and yielded splendid results in the sense of wiping out endemic goitre as a mass disease. By combining general iodised-salt prophylaxis with prophylaxis of children and also other forms of group prophylaxis it is possible to stamp out endemic goitre in a short time.

Parallel with prophylactic work, the treatment of patients with endemic goitre continues. It is necessary even if the incidence of new cases is reduced to naught since usually in goitrogenous regions there are patients with endemic goitre which originated prior to the iodine prophylaxis campaign. Treatment of such patients by conservative and surgical methods ensures the complete stamping out of goitre in the given locality.

The rich experience in studying the clinical manifestations and pathomorphology of endemic goitre, both diffuse and nodular, beginning with its early stages and ending with crude and regressive changes of the thyroid tissue, shows that at different stages of goitre development treatment must not be the same. Yet to this day iodine therapy of goitre is still widely used at a stage in the process when this treatment cannot be effective. Iodine in the physiologically needed dose, ensuring the normal iodine balance, can be effective when it is used for medication only in the very early stage of goitre development expressed merely in thyroid enlargement, i.e., diffusive hyperplasia which did not attain a large degree. True, in conditions of a goitrogenous region, inasmuch as the aetiological factor operates constantly, the use of the physiologically required quantities of iodine is undoubtedly justified aetiologically and pathogenically. Since iodine therapy produces definite results even in somewhat increased dosage (but under no circumstances in the form of Lugol's solution or an iodine tincture in a dose of from 1 to 15 drops, as is done at times; this must be categorically prohibited), there are no grounds for rejecting its use.

There are, however, other views as well which reject

iodine therapy of endemic goitre, notwithstanding its age-old history, beginning with the use of sea cabbage, burned sponge and other iodine-containing products. Janet wrote in 1958 that in all cases of endemic goitre one should avoid administering iodine, "the witness of an old heresy which it is hard to refute". A number of authors draws attention to the possibility not only of inducing so-called Jod-Basedow by the excessive dosage of iodine, but also of developing iodine thyroiditis and a number of allergic phenomena that unfavourably affect the general state of the patient and the condition of the thyroid tissue, which subsequently responds hard to treatment in general.

Janet also objected to the use of synthetic antithyroid preparations (methylthiouracil and others) in endemic goitre, with which we agree. Since radioiodine therapy has become widespread, it is necessary to point out that the latter is inapplicable in endemic goitre even when it is accompanied by thyrotoxic symptoms.

The complications in iodine therapy include not only pronounced forms of Jod-Basedow, but also mild symptoms of hyperthyroidism or even pronounced thyrotoxicosis which develop in patients with euthyroid goitre after the use of iodine preparations. That is why the application of iodine in endemic goitre requires great caution. Janet's view coincides with the statements of many authors (Matovinović and Ramalingaswami) who consider the hormonal treatment of endemic goitre with thyroxin or thyroidin much more substantiated. We wrote about the advisability of this medication as early as 1933 on the basis of experience in treating school children in Samarkand and the positive results obtained from the use of thyroidin among a large number of people we had under observation in 1930. The experience we accumulated shows that patients stand well the ingestion of thyroidin in a dose of from 0.01 to 0.1 g daily or every other day, that this does not induce hyperthyroid symptoms and, consequently, can be used for a long time.

A comparative appraisal of the results of iodine and thyroidin therapy has shown the considerably greater efficacy of the latter; thyroidin medication is fully permissible not only in hypothyroid forms of goitre but also in the euthyroid state.

It is interesting that, according to data cited by Matovinović and Ramalingaswami, treatment of goitre with thyroidin was known already in the Middle Ages and that at present it has received theoretical substantiation from the positions of both the view on the role of the thyrotropic hormone and its influence on the thyroid and the view on the compensatory hypoplasia of the endocrinal organ when the organism receives a surplus of the respective hormone. The effect of thyroidin is especially favourable in diffuse forms of endemic goitre and also in some forms of polycystic or conglomerate nodular goitre of soft consistency without big destructive alterations. If the destructive changes are considerable conservative treatment even with thyroidin naturally produces no results. In the surgical clinic thyroidin treatment might be undertaken by way of preoperative preparation; in patients with a large goitre (IV and V degrees) thyroidin leads to an involution of the goitre, which is particularly important for easing the operation in intrathoracic goitres which are wedged into the upper thoracic aperture.

After treatment with thyroidin the size of a large goitre is involuted by half or even by two-thirds and the operation, which at first seemed complicated and even dangerous, becomes technically more simple and it is easier for the patient to undergo it. In thyroidin treatment, which frequently the patients stand better than thyroxin, it is always necessary to ascertain the limit of tolerance to the preparation, beginning with large doses, then going over to doses of optimal efficacy and to small, maintenance doses which can be ingested for years without any complications as goitre prophylaxis when there is no iodine prophylaxis. Of course, careful watch over the patient is

needed, but such medication does not have the dangers inherent in iodine therapy. Complications of the latter depend at times on individual sensitivity to iodine and also on the dosage. Large doses of iodine, exceeding the daily physiological requirement of the organism many times over (300-1,500 mg daily and higher), which erroneously are called microdoses, according to data of Matovinović and Ramalingaswami, cause a higher secretion of the thyrotropic hormone by the hypophysis and phenomena of hyperthyroidism not only in case of euthyroid goitre, but also in patients with hypothyroidism.

Studies made by Clements have shown that in many cretins, although the thyroid absorbs iodine actively, the latter is not turned into an organic compound of full value for the organism. The iodine circulates in the blood and, being bound with proteins, is not thyroxin. Nevertheless, thyroid preparations, as a rule, produce a definite effect in cretins, which points to the extremely low content of the active thyroid hormone in the blood.

It follows from the aforesaid that the wide and prolonged use of microdoses of iodine in pills or in the form of Lugol's solution in patients with endemic goitre should be revised. Evidently it will be proper to consider that in goitrogenous regions, owing to the wide use of iodine therapy, there is a growing number of patients with a hyperthyroid form of goitre that responds with great difficulty to hormonal medication. To our regret, so far there is no well documented study based on extensive material which would present with complete objectivity the results of the use of iodine microdoses not only in endemic goitre, but in thyrotoxicosis as well. This particularly applies to iodine therapy of nodular forms of goitre with large destructive alterations and the formation of cysts and proliferation of the connective tissue, which cannot be cured by conservative iodine therapy, but are even hardly involuted by thyroidin medication.

In general nodular goitre should be regarded in the

oncological aspect and only in a few cases is it permissible, before deciding on surgical treatment, to try thyroidin medication. The need for surgical intervention, on the other hand, is dictated by the fact that a nodular goitre might become the source of malignant degeneration, with the danger of cancerisation increasing with the duration of the disease. Almost every patient with a nodular form of goitre should undergo surgical treatment. This premise has become the main principle of medical practice in the Soviet Union and other countries. This should put an end to the futile use of iodine pills in nodular goitre with destructive alterations. Surgical treatment of endemic goitre has now reached such a degree of perfection that timely intervention is practically safe and produces almost no complications; relapses are observed in an insignificant percentage of cases, chiefly in multiple conglomerate nodular goitre.

Data on postoperative lethality for the past 100 years are of interest. Thus, in 1850, when operations for goitre were prohibited in France postoperative lethality reached 41 per cent. In 1883, it declined to 12.8 per cent, in 1910, to 3.2 per cent, in 1941, to 0.76 per cent and in 1958, to less than 0.2 per cent (data given in the bulletin of the World Health Organisation). It should be noted that, according to our data, of the more than 3,500 patients operated for nodular and sporadic goitre, we lost only one (lethality of 0.06 per cent) in 1934, in Nalchik, as a result of emboly of the pulmonary artery. Consequently, in our personal statistics, postoperative lethality is even lower than the figure cited in the bulletin of the World Health Organisation.

Our method of operation for goitre, described in detail in Chapter VII, is applied more and more widely in the Soviet Union and in some People's Democracies. It yields a minimum of complications, specifically damage of the parathyroid glands and laryngeal nerves. Surgical treatment plays a big part in the drive against goitre by

eliminating the remnants of goitre endemy: iodine prophylaxis reduces the incidence of the disease to naught among the growing generation, while surgical intervention stamps out endemic goitre among adults as well.

The Soviet network of antigoitre institutions—dispensaries and stations—is directed by the antigoitre committees in the public health ministries and regional health agencies. These committees consist of the chief specialist, therapeutist, surgeon, representatives of the sanitary and epidemiological service, organisations of sanitary enlightenment, the food industry, departments of medical institutes and antigoitre dispensaries. The antigoitre campaign, in which the country's entire medical network takes part, is conducted in accordance with plans drawn up by the antigoitre committees (co-ordinated by the Central Antigoitre Commission of the U.S.S.R. Public Health Ministry and the organisational methodological department of the All-Union Institute of Experimental Endocrinology) and approved by the Councils of Ministers of the republics and also by regional executive committees. All antigoitre work is methodologically directed and controlled by the local antigoitre committees and the Central Antigoitre Commission. Experience is exchanged, the results of the work done are summed up and new plans are discussed at countrywide antigoitre conferences, sessions sponsored by the All-Union Institute of Experimental Endocrinology to examine problems of the antigoitre campaign and also at numerous special republican and regional scientific conferences held in different parts of the country.

Many departments of medical institutes and special endemic pathology institutes are conducting goitre research, particularly in the aspect of the unity of the organism and the environment, trace elements, the use of radioactive elements for solving special questions of the pathogenesis of endemic goitre and in other aspects of the goitre problem. Research work is conducted in close co-ordination

with the treatment and prophylaxis of endemic goitre in the Soviet Union.

The task set now is to stamp out in the next few years endemic goitre in the places where it was most widespread in the past, to bring to light areas of endemic thyroid enlargement in order to extend antigoitre measures in these areas of slight endemicity.

CHAPTER VI

MALIGNANT NEOPLASMS OF THE THYROID

The genesis of thyroid malignant neoplasms is governed by laws which are general for malignant tumours, although they have their own distinctions. These distinctions depend on the structure and function of the thyroid as an internal secretion gland and the specific exogenic (in the first place the influx of iodine into the organism) and endogenic (thyrotropic hormone, etc.) influences on the thyroid. The synthesis and incretion of the iodine-containing hormone, thyroxin, which plays an exceptionally important part in the basic processes of tissue respiration, evidently affects especially not only the frequency of thyroid malignant neoplasms, but also their structure and course.

The so-called metastasising adenoma of the thyroid, described for the first time by Conheim in 1876, furnishes an example of the specific nature of thyroid malignant neoplasms. For its ability to metastasise this neoplasm in no way differs from malignant tumours. For its clinical course already Kocher classed such adenoma as a malignant neoplasm. But for its histological structure a metastasising adenoma does not reveal the usual signs of malignity. The morphological criteria are insufficient for establishing the malignant nature of the neoplasm. More than that, the absence of proliferative phenomena which lead to infiltrating growth, the absence of atypism in the cells and figures of mitotic division of the cells, while the structure of the

thyroid presents a normal picture, is frequently typical not only of the main neoplasm, but also of its metastases. In 1939, S. A. Kholdin called these neoplasms "angiophilial" or "haemophilial" adenomas in view of their ability to metastasise in distant parts of the body.

Of great interest is the fact that tissue of metastases of this type of neoplasm preserves the hormonal (perhaps, possibly distorted) function and the ability actively to absorb iodine, which is very important for diagnosing the metastases with the help of radioiodine and for treating this form of tumour. Metastases of thyroid neoplasms with infiltrating growth and a structure typical of malignant tumours, lose their hormonal function in large degree or completely, although as a result of processes of disintegration temporary phenomena of thyrotoxicosis may be observed. But, on the one hand, such thyrotoxicosis, evidently, is not necessarily a manifestation of elevated hormonal function of the thyroid or the neoplasm and consequently a result of hyperthyroidism; on the other, the records of the vast number of patients with diffuse primary thyrotoxic goitre, observed in the All-Union Institute of Experimental Endocrinology, make it possible to assert that this disease prevents the development of malignant neoplasms of the thyroid and possibly of other organs as well.

Among the many thousands of such patients we have not come upon a single case of cancer of the thyroid (except one insufficiently verified and inconclusive observation) and only in one patient have we seen cancer of the pancreas. These assertions fully coincide with the data of other observations, specifically of pathoanatomists (Wegelin), and also with our investigations which demonstrated the greater frequency of cancer of the thyroid among patients in goitrogenous regions than in non-goitrous areas. It is pointed out that cancer of the thyroid occurs from 10 to 30 times more frequently in goitrogenous regions than in non-goitrous areas. It is held that nodular

or adenomatous goitre offers favourable grounds for malignisation. True, this viewpoint is challenged by some investigators, which is mentioned by Clements.

The study of experimental thyroid neoplasms, undertaken on a wide scale in recent years, has lifted the curtain on many hitherto unknown aspects of malignant neoplasms of this endocrinal gland. Thus, the formation of a nodular goitre in conditions of iodine deficiency in nature, considered in the oncological aspect, receives a definite explanation thanks to the experimental inducement of thyroid neoplasms in animals kept on an "iodine-poor" diet.

Many authors (data of the survey by N. P. Napalkov) obtained experimental thyroid neoplasms both under the influence of iodine deficiency and the direct effect of the thyrotropic hormone, whose action was intensified by an iodine-poor diet. It is possible experimentally to induce not only benign tumours of the thyroid which absorb iodine well, but also real malignant neoplasms, incapable of fixing radioiodine.

Disclosure of the mechanism of inducing thyroid neoplasms made it possible to evaluate in a new way the action of anti-thyroid substances of the thiourea group. Purves and Griensbach were the first to obtain experimental thyroid malignant neoplasms under the influence of thiourea. Even when the degree of malignity was not high, these neoplasms produced metastases, although under the influence of thyroxin the development of such neoplasms was reversed. In 1957, A. I. Gnatyshek obtained, with the aid of 6-methylthiouracil, thyroid malignant neoplasms with proliferative growth. It should be noted that still earlier, in 1953-1954 Clausen, using thiouracil, obtained a Hashimoto's struma which then turned into a Riedel's fibrous struma. Of exceptional interest among the many experiments in this field is the work of Moore with his collaborators who demonstrated the possibility of inducing, under the prolonged influence of propylthiouracil, cancer

of the thyroid which invaded the blood and lymphatic vessels and produced metastases in the lungs.

Most authors hold that thyroid malignant neoplasms obtained experimentally have a hypophyseal genesis. Numerous experimental studies have shown that thyroid malignant neoplasms, caused by cancerigenic substances, can be induced easier when using simultaneously antithyroid substances which stimulate the action of the thyrotropic hormone. More than that, malignisation of adenomas is determined by prolonged hormonal stimulation. These observations have been checked and corroborated and it was noted that doses of I^{131} equal to 10-25 μC exert a cancerigenic effect. In experiments conducted by Goldberg and Chaikoff, cancer of the thyroid was formed in 7 out of 25 rats 1.5-2 years after they had received a single dose of 400 μC of I^{131}. A number of authors noted that the combined administration of I^{131} and methylthiouracil resulted in the more frequent formation of neoplasms. There are observations showing that by using I^{131} it is possible to induce in sheep a thyroid malignant neoplasm of the fibrosarcoma type. Marks, George and Bustad point out that the employment of antithyroid preparations in clinical practice may lead to the development of tumours in the thyroid, especially if the patient simultaneously receives radiation therapy. The experiments conducted by N. P. Napalkov not only confirmed these observations, but also made it possible to draw a number of conclusions about the genesis of thyroid neoplasms and particularly to demonstrate with great conclusiveness the role of disturbances of metabolic processes which accompany alterations of the hormonal balance and the influence of other cancerigenic factors.

The existing unanimity of views on the role of the thyrotropic hormone in the genesis of experimental thyroid neoplasms should make us regard with utmost earnestness nodular endemic goitre and not look upon it merely as a cosmetic drawback. To begin with, the strumogenic activ-

ity of the hypophysis plays a part in the pathogenesis of nodular goitre and evidently this explains the characteristic feature of endemic goitre in which the nodular form is so frequent. We pointed out earlier that nodular goitres are seen most frequently in goitrogenous regions, especially with unfavourable sanitary-hygienic conditions, in which the probability of a toxic influence on the nervous system rises and the probability of disturbances of its trophic function grows. On the other hand, the changes in the intraglandular nerve network in case of goitre could determine the atypical proliferative processes, just as the destructive processes. Moreover, regarding nodular goitre as a benign blastoma we must bear in mind the warning of L. M. Shabad, noted Soviet oncologist, that "... each cancer has its precancer". That is why in each case of a thyroid malignant neoplasm we should allow the earlier existence of an anatomophysiological substratum which for a certain time was a precancer. But besides nodular goitre, focci of microscopic proliferation of thyroid tissue or its partial destruction under the influence of various factors (iodine deficiency, anti-thyroid preparations, radioiodine, etc.) could constitute such precancer formations.

From the above data the conclusion can be drawn that, inasmuch as the thyrotropic hormone causes proliferative hyperplastic processes in the thyroid, the cancerigenic factors which induce malignant neoplasms receive most favourable possibilities for action in conditions of endemic goitre which has a tendency to hypothyroidism. But how should we assess the data in literature testifying to frequent cases of cancer in thyrotoxic adenomas? Do they refute what we said earlier about the "anticancer" action of thyroxin and extreme rarity of malignant neoplasms in patients with primary thyrotoxic diffuse goitre? Evidently, the answer should be negative since at present data are accumulating that thyroid neoplasms can secrete into the blood protein products which differ from the normal

thyroid hormone, do not resemble thyroxin and not even triiodothyronine. It may be assumed that the toxic action in nodular goitre depends on the abnormal products of hormonal synthesis. This question demands further study and verification. But regardless of the results it should be stressed that iodine deficiency in itself, as a factor of the environment depressing the normal synthesis of the thyroid hormone, facilitates the formation and development of adenomas, i.e., of thyroid neoplasms that can assume a malignant nature, which fully conforms to numerous endemiological data and the observations of our clinic.

Several principles underlie the modern classification of thyroid malignant neoplasms. The most important of them are the pathogenic and pathohistological. Some classifications are based on functional and aetiological principles. Cancer, sarcoma and rare neoplasm groups should be differentiated in the main.

The first group—thyroid cancer tumours—includes papillary adenocarcinomas and cystadenomas with infiltrating growth, alveolar adenomacarcinomas, small cell and giant cell carcinomas, and also Hürthle cell carcinomas and, lastly, squamous cell carcinoma. Among the sarcomas are differentiated small cell, giant cell and spindle cell sarcomas and fibrosarcomas. Lastly, neoplasms are singled out which are more or less malignant for their course or are capable of metastasising. The most frequent of them are the metastasising adenoma without signs of infiltrating growth, embryonal Wilson adenoma, noncapsulated Graham sclerotic neoplasm, Langhans neoplasm and hemangioendiothelioma.

The clinical picture of thyroid malignant neoplasms also has its specific features manifested above all in that frequently it is characterised by a quite favourable prolonged course without metastases and even the absence of relapses after insufficiently radical intervention. In some cases, on the contrary, the tumours lead to the quick death of the patients. Nevertheless, one gets the impression that a rel-

atively early operation in case of a tumour, diagnosed prior to the operation or accidentally discovered in a histological study of a resected goitre, can give fully satisfactory results even in intervention which only consisted in enucleation of the neoplasm or its extirpation, while leaving not only the second, healthy half of the thyroid but even part of the lobe from which the tumour has been removed. The same may be said about neoplasms, the full excision of which somehow proved impossible. The role of the correlative connections of the thyrotropic function of the hypophysis and the hormonal function of the thyroid itself are revealed both in experiments and in the clinic. While the first facilitates the action of cancerigenic substances, the second inhibits their action not only directly, but evidently, by causing secondarily (particularly in hyperfunction) a decrease in the formation of the thyrotropic hormone which, as we have seen in experimental studies, stimulates the rise of malignant neoplasms. It is held that the thyrotropic hormone promotes the penetration of the cell by cancerigenic substances owing to disturbance of the protective barriers and to intramolecular changes which cause atypical growth of the cell (Rondoni, Dargent, Guinet).

That is why a cautious approach in each case of endemic nodular or sporadic goitre can help in the early diagnosis of thyroid malignant neoplasms. Naturally, the very early stages of cancerous degeneration cannot be detected, but anamnestic data already at a definite stage of the disease can suggest to the physician the possibility of malignisation of the goitre. Thus, if a goitre which has existed for a more or less long time and has been slowly growing for years or has already stopped growing, suddenly begins to increase in size swiftly, malignisation of the goitre may be suspected. The same may be assumed when in a multinodular conglomerate goitre one of the nodules begins to grow swiftly, while the other nodules grow more slowly or not at all. In such cases a change in the con-

sistency of the goitre is noticed; it becomes more dense, although the density might also be a result of destructive processes, fibrosis or even ossification of the tissue in an old goitre. The age of the patient should also be taken into account. Further, as the tumour develops, a number of microsymptoms and then more obvious symptoms of malignity appear in consequence of the neoplasm's infiltrating growth, and invasion of its own capsule and fascial covering. Thus, lesser mobility of the goitre in relation to adjacent tissue, the appearance of irradiating pains behind the ear or in the occiput owing to mechanical irritation of the nerve branches of the cervical plexus, are often a sign of malignant degeneration of the goitre.

The signs of malignity, in addition to density, limited mobility and indistinct boundary of the goitre which, moreover, often becomes tuberous, include steady huskiness of the voice and not infrequently sharp compression of the trachea. Infiltration of the neoplasm masses at times leads to invasion of the walls of the trachea, adjacent muscles and even the subcutaneous cellular tissue. Disintegration of the neoplasmic tissue, which is seen both in cancer and sarcoma, at times stimulates a suppurative strumitis. As a rule, E.S.R. rises sharply, but there is almost no leucocytosis and neutrophilia and the temperature might even remain normal. At first the thyroid malignant neoplasm, as a rule, is not very widespread and always issues from a part of the goitre or one lobe of the thyroid. This fact is of essential diagnostic importance, inasmuch as some forms of thyroid diseases are accompanied by a sharply pronounced density of its tissue, which furnishes grounds for the wrong diagnosis of a malignant goitre. But if the density in the equally diffuse enlarged thyroid is located symmetrically, usually there are no grounds for suspecting a malignant neoplasm. Most often in such cases there is fibrosis of the gland or a chronic Riedel's struma. Even if the thyroid malignant neoplasm has spread to the other lobe of the gland, the infiltrating growth of the

tumour in the place of its initial origin invades large areas of adjacent tissues, causing thereby a corresponding asymmetry of the goitre, full immobility of the gland and often already the development of metastases.

Nevertheless, thyroid malignant neoplasms are not always easily diagnosed, even when there are metastases and also when a malignant goitre develops from ectopic tissue (for example, from an aberrant thyroid which has a special disposition to cancerous degeneration). Only in the latter case might it be useful to make a test of radioiodine uptake. But in general the ability of the tissue of a thyroid neoplasm to absorb radioiodine is sharply reduced.

It follows from the above that when it is impossible to make an exact diagnosis and to establish the time of the malignant degeneration of the goitre, each nodular goitre should be regarded as a precancer formation or neoplasm potentially capable of malignisation. Detection of the malignant degeneration of a goitre is usually belated and the diagnosis is often made when there are already metastases in the cervical lymph nodes, lungs, bones, etc. It is sufficient for the doctor to come upon one such case to abandon the light attitude to an euthyroid nodular goitre as a cosmetic shortcoming, which attitude is often found not only among therapeutists, but at times even among surgeons. Timely surgical treatment of a nodular goitre is a measure preventing malignant neoplasms, although unfortunately in some cases of goitre (conglomerate or multinodular) it is impossible to remove all the small nodules and, moreover, thyroid malignant neoplasms can develop even without a nodular goitre.

The methods of surgical treatment of thyroid malignant neoplasms depend on the degree of development of the tumour, its invasion of the surrounding tissues and the existence of metastases. Subsequent medication also depends on the nature of the malignant neoplasm and, specifically, its type and structure. Hence only one method should hardly be followed. Thus, most surgeons employ

the method of enucleating the goitre nodule and, when suspecting malignity, simultaneously with enucleation they remove the adhering thyroid tissue, particularly its sections closely connected with the nodule or infiltrated by the neoplasm.

In the opinion of most surgeons, enucleation should be made in the early stage of the development of the thyroid malignant neoplasm. Subsequent roentgenotherapy, directed on the region of the operation, is advisable (up to 4,000-6,000 r). When the process has become more widespread, enucleation is combined with wider resection of the thyroid or the full extirpation of the neoplasm with the entire lobe of the thyroid. In such hemistrumectomy there is no need to remove the entire thyroid, i.e., also to remove the opposite healthy lobe of the thyroid. The advisability of complete extirpation of the thyroid is contraindicated by data presented earlier on the role of the thyrotropic hormone, the secretion of which would be increased; on the whole, however, account should be taken of the fact that complete extirpation of the thyroid is antiphysiological from the endocrinological standpoint and hence is irrational. Nevertheless, some authors advise even in the initial stage of the disease to remove the entire thyroid, cervical lymph nodes and, in case of invasion of the neoplasm into the cellular tissue in the region of the mediastinum, also to remove the neoplasmic masses from the mediastinum when cutting the sternum. Since during the extirpation of the entire thyroid gland the parathyroid glands might also be removed, the surgeon tries to find them in the excised tissue and implants them in the subcutaneous cellular tissue.

The scope of surgical intervention is determined by the spread of the neoplasm, its invasion of the muscles, vessels, etc. When operating for initial forms of malignant neoplasms, the desire of the surgeon to remove all the healthy thyroid tissue is also not justified even when subsequent radioiodine therapy is planned. It is held that

if the thyroid tissue is left the radioiodine will not be absorbed sufficiently by the metastases. Such antiphysiological, crippling operations are to some extent permissible when alongside metastases in the cervical lymph nodes (in cancer of metastasising adenoma) there are definite signs of metastases in the bones, lungs and other tissues. In all other cases operations for limited malignant tumours of the thyroid with the full extirpation of the latter cannot be considered justified. The record of the clinic of the All-Union Institute of Experimental Endocrinology shows that in early stages of the development of thyroid neoplasms enucleation of the tumour alone or enucleation in combination with resection of the thyroid lobe and subsequent roentgenotherapy produce splendid results.

Between 1936 and 1958, 73 of the 78 patients with thyroid malignant neoplasms were operated in the surgical department of our clinic. Five patients were transferred to conservative radium treatment in oncological institutions. The age-group distribution of the patients was as follows: up to 10 years, one patient; from 11 to 20, three; from 21 to 30 years, seven; from 31 to 40 years, 22; from 41 to 50 years, 20; from 51 to 60 years, 21; from 61 to 70 years, three; older than 70 years, one patient. Thus, most of the patients were in the adult group, from 31 to 60 years. The distribution of the patients as regards the duration of the goitre disease was as follows: up to six months, seven patients; up to one year, seven; up to two years, six; up to three years, six; up to four years, six; up to five years, three; up to six years, three; up to seven years, five; up to eight years, four; up to nine years, four; up to ten years and more, 27 patients. In 18 patients the goitre of long duration began to grow swiftly a few months before the operation.

Of the 78 patients, 14 were men and 64 women. When the patients entered the clinic none had a thyroid enlargement of the I degree; four had a thyroid enlargement of the II degree; 41, the III degree; 24, the IV degree and

nine, the V degree, i.e., a huge goitre. Sixty-four patients had a one-sided goitre; dense nodules, solitary and multiple, were found in 47 patients. The goitre was almost immobile or its mobility was limited in 58 patients; enlarged cervical lymph nodes were seen in 37; difficulty in respiration up to stridor, in 29 patients; difficulty in swallowing and unpleasant sensation in the region of the oesophagus, in eight patients.

Roentgenoscopy of the thorax and neck revealed a shift or constriction of the trachea in 24 patients; a homogenic shadow in the upper part of the mediastinum was noticed in 13 patients. As distinct from roentgenoscopy data in usual benign nodular goitre, the shadow behind the sternum did not shift when the patient coughed. Formation of a shadow behind the sternum is explained either by the invasion of the neoplasm into the region of the mediastinum or metastases in the lymph nodes.

A study of the blood revealed that in 21 patients the number of erythrocytes dropped to 3,000,000 or 4,000,000, while in 52 patients the number was above 4,000,000. The number of leucocytes ranged from 4,000 to 10,000. E.S.R., as a rule, was somewhat accelerated up to 20-40 mm per hour. There was no special change in the white blood picture.

A study of the basal metabolism revealed its elevation by 15 to 30 per cent in 24 patients; the same patients also had tachycardia. Evidently, this can be connected with temporary phenomena of toxicosis in view of the possible processes of neoplasm disintegration and the absorption of the products of this disintegration.

In the clinic thyroid neoplasms were frequently found to have metastases in the lymph nodes and distant tissues. Thus, 21 patients had enlarged nodes in the region of the neck on the side where the tumour was localised; in four patients the nodes could be observed on both sides of the neck; three patients had metastases in the spinal column, the bones of the pelvis and thigh; two patients had simul-

taneously metastases in the lungs, lymph nodes and other organs. The neoplasm invaded the adjacent tissues and organs in 22 patients; the mediastinum, in 13 patients; the region of the cervical vascular-nerve bundle, in three; the trachea, in one; and the oesophagus, in one patient.

It follows from the above that many patients were admitted into the clinic at a period when the growth of the thyroid malignant neoplasm was not limited to the gland, but also spread to adjacent tissues and was accompanied by metastases. Hence it is not surprising that in many cases the exact diagnosis was made prior to the operation. There were 37 such patients, while in 16 patients malignant neoplasm of the thyroid was suspected. In 25 patients the diagnosis of malignant neoplasm was established either during the operation or in histological study.

According to our data, the number of patients with thyroid malignant neoplasms amounts to about 4 per cent of the total number of patients with nodular goitre operated in the surgical department of the All-Union Institute of Experimental Endocrinology. Comparing this percentage with data in literature we find that it differs from the generally known statistical data. In 1948, V. F. Kolosovskaya found among 439 patients with different forms of goitre a malignant goitre only in 0.45 per cent. In 1957, N. S. Malyugin noted a malignant goitre among 26 out of 650 patients, i.e., 2.4 per cent, while Horn and Dull (1952) observed it in 174 out of 1,777 patients, or in 9.7 per cent. In patients with nodular forms of goitre a higher percentage with malignant goitre has been observed. Thus Lahey, and Hare (1951) found malignant goitre among 198 of the operated 1,971 patients with nodular goitre, or 10 per cent.

Analysing the above data, we must take into account the fact that these percentages do not characterise the frequency of malignant degeneration of nodular goitre. Evidently, the percentage in general is considerably smaller. Inasmuch, however, as exceptional difficulties arise in the

early diagnosis of thyroid malignant neoplasms, it is necessary in each case of nodular goitre to resort, as a rule, to surgical intervention. An operation for nodular goitre is the best method of preventing malignant neoplasms of the thyroid.

Examining our materials of the surgical department of the All-Union Institute of Experimental Endocrinology (processed by F. A. Agafonov), we find that the most frequent method of surgical intervention was the extirpation of the neoplasm together with the regional lymph nodes and the cellular tissue around the tumour. We have made 38 such operations. In cases of invasion of the tumour into the adjacent tissues, muscles, veins or oesophagus wall we extirpated the neoplasm together with the surrounding tissues in 16 patients, removing when possible the neoplasm within the bounds of healthy tissue. Enucleation was made only in ten patients; those were primarily patients in whose case the diagnosis of malignant tumour was made only during histological study. The same should be said about the enucleation of several nodules, made in four patients. When it was impossible to remove the entire neoplasm which infiltrated the cervical organs and the region of the mediastinum, a partial resection of the tumour was made in five patients. It should be added that in seven of the patients we operated we had to make repeated operations. In the case of one patient four operations were made in the course of ten years; originally the neoplasm was removed and then the metastases. Three patients underwent three operations each and the other three patients had two operations each. All the seven patients have preserved their working capacity to this day and some of them are only undergoing repeated prophylactic roentgenotherapy.

All operations were made under local anaesthesis, novocain. During the removal of the neoplasm the sternum was not incised, although in some of the patients the nodules of the neoplasm were removed from the substernum. In

general, of the total number of the operated patients 46 are practically healthy and able to work; 12 of them have been under observation for a year, 19 for three years, ten for five years and five for more than ten years. One of the patients, a woman, has been under our observation for 12 years; she is practically healthy and able to work. In addition to the above 46 patients, ten of operated patients are now undergoing treatment. The results of the combined treatment of these patients, i.e., operation and roentgenotherapy are fully satisfactory; of these patients six were operated three years ago, two, five years ago and two, ten years ago.

Of the total number of 73 operated patients with malignant thyroid neoplasms 17 died at different periods after the operation, i.e., 23.3 per cent. Eleven died during the first year after the operation; three in the next year; two, three years after the operation and one patient, five years later.

These results can be regarded as quite satisfactory if account is taken of the fact that not so long ago there were literally single cases of a favourable outcome of such operations, while the number of operations for thyroid cancer was relatively small. N. G. Tsarikovskaya collected from Russian literature prior to 1953 only 476 such cases, primarily operations in specialised oncological and endocrinological institutions. About 20 years ago V. S. Levit reported as a rare observation the case of a patient who was alive 9 years after having been operated for thyroid cancer by de Quevrain. Let us note in passing that Levit recommended the complete extirpation of the thyroid in malignant neoplasms and the subsequent administration of thyroidin to the patients for the rest of their life. At present the idea of removing the entire thyroid seems absolutely irrational to us, although McDonald and Kotin again propose the extirpation of the whole thyroid and the removal of the regional glands not only in the region of the neck but also in the upper part of the mediastinum, with

the subsequent implantation of the parathyroid glands. At present such operations are recommended to ensure efficacy of radioiodine therapy. But our patients with successful results of surgical treatment underwent only repeated prophylactic roentgenotherapy in the postoperative period and one patient received radium treatment.

In the histological study of the neoplasms removed during the operation cancer without exact differentiation of its type was established in 19 patients; 15 had a metastisising adenoma; ten, an adenocarcinoma; nine, a follicular cancer; seven, papillary cancer; seven, round cell and spindle cell sarcoma; two, medullary sclerotising cancer; one, polymorphous cellular cancer; one, epithelial cancer; one, squamous cell cancer and one patient had a carcinosarcoma. Sarcomas and also follicular and papillary cancer were the most malignant neoplasms. Metastisising adenomas with atypical cells and without infiltrating growth possessed the least degree of malignity.

As pointed out earlier, considerable successes in treating thyroid malignant neoplasms are registered now and the elaboration of methods for early diagnosis are of particular importance. The aim should be to operate on each nodular goitre because experience shows that many patients with thyroid malignant neoplasms apply for medical care in a period when the diagnosis of malignant neoplasm is already indisputable. The rule should be urgently to operate patients with goitre even when there is only suspicion of a malignant tumour. The doctor should bear in mind that by widely employing surgical treatment of nodular goitre he accomplishes a major task in preventing thyroid malignant neoplasms.

CHAPTER VII

SURGICAL TREATMENT OF THYROID DISEASES

History

The present chapter deals with the surgical treatment of two of the most widespread thyroid diseases—endemic goitre and primary toxic diffuse goitre, also known as Basedow's disease or thyrotoxicosis. We have in mind that surgical treatment of sporadic goitre (as a rule, nodular) hardly differs from the treatment of nodular endemic goitre. Surgical treatment of thyroid malignant neoplasms has been examined in the previous chapter. The surgical treatment of thyroiditis (Riedel's and Hashimoto's strumas), cysts of the thyroglossal duct and some other rare diseases is a special subject. For the lack of space we do not examine these questions and refer the reader to other sources in literature.

When considering surgical treatment of thyroid diseases, it is necessary first of all to bear in mind the physiological importance of this gland and the intricacy of the topographo-anatomical conditions in which it is located, in the first place, the important adjacent cervical organs (parathyroid glands, laryngeal nerves, trachea, large vessels, oesophagus, etc.), whose injury could cause not only temporary, at times extremely dangerous, complications, but also stable grave consequences. The rules of surgical deontology are especially applicable to surgery of the thyroid, just as to surgery of endocrinal glands in general.

Success of surgical treatment of patients with endemic goitre, especially with primary thyrotoxicosis, depends not on the number of the thyroid operations made by the surgeon. Experience should merely supplement the exact and deep knowledge, keen sense of observation, ingenuity, swift reaction to unexpected difficulties, concentrated attention throughout the operation and the thoughtful choice of the most advisable operation. It is in place here to recall the statement of N. N. Petrov, eminent Soviet oncologist, about the experience of surgical treatment which should be enriched "at the expense of the surgeon's own work, his proper training, and not at the expense of the operated patients through daring greater than skill".

In this training of a surgeon who is able to think in clinical terms and has a broad biological outlook, it is particularly important to combine deep knowledge of the clinical picture, pathological anatomy and pathohistology of endocrinal diseases with excellent knowledge of topographical anatomy and physiology and mastery of fine and precise operation techniques.

The technique of the surgeon and his thoughtful attitude to each detail of the operation are of vital importance, particularly if he wants to change the widespread opinion of goitre operation as a "bloody" and especially dangerous operation. It is in place here to recall the words of Mackas, who wrote about surgical intervention in goitre: "A goitre operation can be a very easy and also a very grave intervention; a good result can be achieved only in case of perfect aseptics and mastery of surgical technique. The close proximity and threat of injury to important formations can be fatal for the operated person. Not infrequently there are critical situations when the patients are threatened with death from asphyxia and haemorrhage and then only cool-headedness and the swift action of the surgeon can save the day." These few words reflect the diverse situations in which the surgeon may find himself.

Experience gained in thyroid surgery is also of great importance when there is proper knowledge and thorough consideration for the methods of operation, in addition to the surgeon's qualities of which Mackas spoke. It is natural that a surgeon with much experience, who more than once coped with sudden complications, will not be lost when faced with new difficulties that cannot always be foreseen; a goitre operation is a kind of test, particularly of the technical skill and theoretical knowledge of the surgeon who after this acquires, but sometimes also loses, the taste for this kind of intervention, readily passing on patients with goitre to other specialised medical institutions. We regard such a way as incorrect because study of modern methods of goitre operations enables any surgeon who has mastered "big surgery" to operate for goitre.

Having mastered the methods of operating for a "simple" goitre, a surgeon can undertake operations for primary thyrotoxicosis (Basedow's disease). This sequence in the mastery of thyroid surgery was mentioned by A. V. Martynov who 50 years ago proposed his original modification of the wedge-shaped resection of the thyroid. Modern methods have far advanced as compared with that form of intervention and it seems to us advisable to present a brief sketch of the history of thyroid surgery.

In the first stages of thyroid surgery, when anaesthesia, antiseptics and aseptics were unknown, endocrinology did not exist as a science. The methods of operation then were very primitive; surgical treatment of goitre represented such a dark page in the history of surgery that, for example, in France about 100 years ago operations for goitre were even prohibited. But in 1847, N. I. Pirogov in Vladikavkaz and in 1850, A. A. Milavsky in the Urals for the first time made successful operations for endemic goitre. In Ekaterinburg a sick worker was even paid by the factory management ten rubles, a considerable sum in those days, for his consent to undergo a goitre operation (Tikhov).

The use of ether anaesthesia already began at that time and, with the introduction of antiseptics, Lister in 1871 made the first operation in the world for Basedow's disease. In that period and subsequently goitre surgery was widely developed (Kocher, Reverdin, Mikulić, Wölfler, Tilloau, Ren and others). In 1893, I. D. Sarychev performed in Moscow the first operation for Basedow's disease in Russia. As surgery developed and knowledge of the anatomy and physiology of the thyroid and parathyroid glands was extended, postoperative results improved considerably and grave complications (tetany, hypothyroidal cachexia and myxoedema) became more rare and postoperative lethality declined. Exothyropexia, complete extirpation, scooping out of the goitre nodules and ligation of the vessels were replaced by resection and enucleation of the affected sections of the thyroid. Operations for goitre and for Basedow's disease became increasingly widespread in Russia at the end of the last and beginning of the present century.

The development of thyroid surgery in Russia is associated with the names of many surgeons (V. I. Razumovsky, P. I. Dyakonov, N. A. Velyaminov, A. A. Bobrov, I. K. Spizharny, S. P. Fyodorov, Zoege von Manteufel, A. A. Brzhozovsky, A. V. Martynov, M. N. Shevandin, L. V. Lepeshinsky and many others). Surgical treatment of Basedow's disease was already one of the basic items on the agenda of the 10th (1910) and 17th (1925) congresses of Russian surgeons. It was widely examined at the 17th Congress (A. V. Martynov, O. S. Bokastova, V. A. Lyapustin, N. N. Petrov, V. N. Rozanov, S. I. Spasokukotsky, V. S. Levit, V. V. Uspensky, V. A. Oppel). The one-stage bilateral resection, according to Martynov, without ligation of the inferior thyroid artery was recommended, with the subsequent stitching by a continuous suture of both resected lobes of the thyroid. Nevertheless, the use of other methods, now already obsolete, was continued. Even now in Basedow's disease some surgeons make a

one-sided extirpation with a wedge-shaped resection of the second lobe, preserving the isthmus of the thyroid and making a ligation at a distance of three or four arteries of the thyroid. Until recently some surgeons made a two-sided extirpation leaving the isthmus. Frequent complications, high postoperative lethality and a considerable percentage of relapses in such operations directed the attention of surgeons to the preoperative preparation of the patients as the chief factor of success. Indeed, the introduction of iodine preparation (on the proposal made by Plummer in 1921) considerably reduced postoperative lethality thanks to a reduction in postoperative thyrotoxicosis. This shifted the attention of surgeons exclusively to questions of preoperative preparation because at that time it seemed that improvement of the methods of operation had reached the limit. Today, too, not infrequently the success of surgical treatment of thyrotoxicosis is credited to preoperative medication. This undoubtedly is an underestimation of the importance of improving the method of operation and its technique.

As a result of further development and improvements, which will be discussed subsequently, thyroid surgery in our country has developed in recent decades not only in clinics but also in many city hospitals.

Inasmuch as surgical treatment of endemic (and sporadic) goitre began much earlier than that of Basedow's disease we shall examine in the same sequence the indications, methods and results of surgical treatment of these diseases.

Surgical Treatment of Endemic Goitre

Surgical treatment of endemic goitre is an important method of antigoitre struggle. It is highly effective and, when used in good time and correctly, is practically safe. Suffice it to say, as we already mentioned in Chapter V, that in over 3,500 operations for simple goitre we lost

one patient with a huge goitre a few days after the operation from emboly of the pulmonary artery. This, by the way, does not mean that in general an operation for goitre can be regarded as absolutely safe intervention. Among a number of surgeons lethality in operations for goitre reaches 1-2 per cent and even more.

Surgical treatment of goitre is indicated when conservative medication is ineffective and primarily in all nodular forms, regardless of the presence of functional disorders. In diffuse goitre it is indicated in cases of thyrotoxicosis that do not respond to conservative medication and in compression of the trachea and other cervical organs. Mechanical compression of important cervical organs and also thyrotoxic phenomena and, the more so, suspicion of malignant degeneration of the goitre are absolute indications for an urgent operation.

In fact, the nodular, i.e., adenomatous nature of the goitre predetermines the surgical method of treatment and the only question is whether it is possible to postpone the operation for some or other reason. In nodular goitre with symptoms of hypothyroidism surgical intervention, designed to remove the goitre, can not only check the further development of hypothyroidism, but also remove it completely as a result of improved blood circulation in the remaining thyroid tissue and elevated function of the tissue in the remnant which regenerates after the operation. In some cases such patients should be treated with thyroidin before the operation, which can involute the goitre considerably and make easier the performance of the operation. It is expedient to do this even in the case of cretins, among whom a favourable effect of the described combined treatment is possible.

At first glance this might seem very unlikely. But in reality removal of the goitre nodules has deep pathogenetic reasons. The point is that each goitre nodule, when its action is considered from the positions of the cortico-visceral theory of disease, represents an irritation focus.

Deep morphological alterations, specifically of the intraglandular nerve network, cannot but cause alterations of afferent signalisation. Hence by removing the focus of pathological afferent impulses through the enucleation of the goitre nodule, we not only improve the condition of the surrounding thyroid tissue, but also remove pathological reflexes. More than that, the greater the change in the structure of the endocrinal gland, the more grounds for change and distortion in the synthesis of the normal hormone, all the more since we cannot reduce the entire pathology of an endocrinal gland to a simplified scheme of hypo- or hyperfunction. From this standpoint, too, it is understandable that the removal of pathological tissue, i.e., of the goitrously altered tissue from which the goitre is made up, is fully justified. Moreover, such removal is of prophylactic anticancer significance, inasmuch as each nodular goitre is considered by contemporary endocrinology in the oncological aspect. Thyroid adenomas have all the signs of neoplasms, proliferative phenomena of the epithelium easily arise in them and the epithelium can acquire atypical and, lastly, malignant growth.

In each case of nodular goitre thought should be given to the time of surgical intervention. This question is decided depending on the nature and size of the goitre, its consistency, mobility, location, intensity of growth, age of the patient and also his attitude to the disease and a number of other factors.

An easily removed nodular goitre in patients above 30 or 40 years of age should be operated upon unhesitatingly. Considered in the aspect of an oncological problem, a nodular goitre in many other cases too should be operated upon after short preparatory preoperative treatment, usually conducted outside the clinic. An attempt to cure goitre with thyroidin can be made only in the case of so-called conglomerate goitres of soft consistency. Separate cases of early one-sided nodular goitre of soft consistency which do not show a tendency to noticeable growth may

also be treated with thyroidin, considering this medication as a trial or as preoperative preparation.

In goitrogenous regions the doctor can always single out among patients with goitre (who apply for medical care themselves or are revealed during examinations of the population) those who are in need of an operation in the first place and those who can remain under observation for a time. A proper decision about absolute and relative indications for an operation and its date largely depend on a thoughtful study of each patient and the experience of the surgeon. The only essential thing is that all patients with nodular goitre should be placed under observation of a surgeon because experience shows that failure to abide by this demand may tragically worsen the patient's condition. In fact, each patient with nodular goitre should be dispensarised and placed under doctor's control.

The attitude to euthyroid diffuse endemic goitre should be different. In case of diffuse endemic goitre with minor alterations of the thyroid tissue, i.e., in the first phase of strumous hyperplasia, an operation is inadvisable. Nevertheless, in the works of some surgeons there still are descriptions of operations on patients with diffuse euthyroid goitre. It should be noted with satisfaction that in recent years such operations are absent almost entirely. Reher rightly considers that surgical intervention in diffuse euthyroid goitre or so-called large thyroid is a "sign of the surgeon's insufficient intelligence". Nevertheless, in some cases of euthyroid of long duration or even hypothyroid diffuse goitre with pronounced destructive alterations, justification for surgical treatment can be found, but only after inefficacy of persistent conservative medication and only when the goitre causes a threatening compression of the trachea and considerable difficulty in swallowing. Incidentally, when the goitre reaches such large dimensions and such phenomena appear, it is difficult to imagine that it is purely diffuse. Most probably, such a goitre is already of a mixed character, i.e., has nodules. Conservative treat-

ment of diffuse goitre is not limited to the use of iodine. The modern viewpoint, discussed earlier, practically rejects the expediency of treating endemic goitre with iodine, considering it suitable only for the prophylaxis of goitre. As for treatment of euthyroid and hypothyroid endemic goitre and of diffuse goitre in particular, as we pointed out earlier, thyroidin should be used. This can yield splendid results and protect the patients from unnecessary operations. Only in case of substantial destructive alterations in "aged" goitres, particularly in mixed forms, the results of thyroidin medication will be very modest or even imperceptible for the patient. Naturally, in diffuse goitre with thyrotoxicosis, the question of indications for an operation is considered in an entirely different light and in this case one should be guided mainly by the indications which will be discussed when describing surgical treatment of primary thyrotoxicosis.

Going over to the methods of operation for endemic goitre, it should be said that for a long time the method most frequently used was bilateral resection and also resection combined with enucleation and accompanied by the ligation of one to three thyroid arteries, possibly closer to the thyroid tissue or "at a distance", i.e., far from the thyroid. In one-sided goitres (when the opposite lobe of the thyroid is normal) one-sided resection with ligation of the artery on one side was used. In a two-sided goitre some surgeons ligated all the four thyroid arteries.

In 1931, V. S. Levit conducted a poll of Soviet surgeons, most of whom informed him that they operate on a goitre without ligation of the inferior thyroid arteries at a distance. Levit pointed out that in non-goitrous regions there was no need to ligate all the four arteries. Frequently it is enough to ligate the two superior thyroid arteries. In Irkutsk Levit saw a goitre relapse even after a radical operation with the ligation of the four vessels.

The poll conducted in 1951 by D. V. Anikandrov revealed that many Soviet surgeons had gone over to the new

method of operation elaborated by us and, consequently, do not make the above-mentioned ligation of the thyroid arteries. Our method calls for ligation only of the branches of the thyroid arteries in the visceral layer of the 4th fascia of Shevkunenko (3rd fascia of Pirogov) which covers the thyroid, and for ligation, in the tissue of the remnant, of the branches penetrating the enucleated adenomatous nodules. At present an operation for nodular goitre more often consists of enucleation in combination with a large or small resection of the thyroid tissue surrounding the goitre, depending on the degree of its hyperplasia or atrophy.

Operations for endemic goitre are made under local anaesthesia, without special iodine preparation of the patient accepted at present in the case of patients with Basedow's disease. In a goitre of huge size (V degree) it is at times useful to administer thyroidin before the operation to involute the goitre. We use an infiltration anaesthesia of 0.25-0.5 per cent solution of novocain (without adrenalin) with supplementary anaesthesia in the process of operation (after Vishnevsky). L. V. Lepeshinsky used a general inhalation anaesthesia, although he admitted that local anaesthesia is preferable. Progress in the technique of anaesthesia and the use of medicamentous hibernation with the employment of neuroplegic ganglioblocking means in present-day conditions have given some surgeons reasons for resuming general anaesthesia in thyroid operations. However, as a rule, there is no need for this not only in endemic, but also in thyrotoxic goitre.

Here is a brief description of our method of operation for nodular goitre.

A small transverse or slightly crescentic incision of the skin of the neck is made corresponding to the location of the goitre and its size. After ligation of the subcutaneous blood vessels the sternohyoid muscles are incised, while the sternothyroideus muscles are pushed aside, incising them only in exceptional cases. As a result of novocain infil-

tration and the corresponding hydraulic preparation of the tissues, the goitre separates very easily and anatomically. The goitre is bared and then it is fully luxated from the wound at once or gradually, after partially catching and incising the visceral layer of the goitre-covering 4th fascia of Shevkunenko; the vascular branches which run through the fascia are caught and incised on the goitre itself. In case of complete atrophy of the thyroid tissue covering the goitre, nodule enucleation begins with the catching and incision of these vascular branches. If the goitre nodule or nodules are surrounded by a mass of hyperplastic tissue, after partial incision of the above vascular branches together with the fascia, the goitre becomes fully luxated from the wound and remains connected only with the trachea and the other underlying tissues (the vessels and fascia layers passing into the region of the vascular bundle and also with the loose cellular tissue between the trachea and the oesophagus). After this, the surgeon grips with Billroth's clamps consecutively not only the arterial and venous branches, together with the fascia layers covering the thyroid, but also the thyroid tissue adhering to the goitre nodules. The latter tissue is cut across up to the capsule of the nodules which are separated (at times by gauze) so that the little-altered thyroid tissue should remain for forming the remnant. All the branches of vessels going into the nodules which bleed (or could bleed) are consecutively gripped by haemostats. This makes it possible to enucleate the goitre nodules almost bloodlessly; part of the resected slightly altered, atrophied or diffusely hyperplastic thyroid tissue is carried away together with the nodules. Frequently the enucleation of the goitre nodules proceeds so easily that it is necessary very swiftly to clamp with haemostats the thyroid tissue to prevent or stop haemorrhage. Incidentally, as soon as the entire goitre is gripped by hand (and gauze), we press down the blood vessels with fingers pushed under the entire lobe of the

thyroid, which makes the operation bloodless. Such a method leaves the region where the parathyroid glands and the laryngeal nerve are located outside surgical manipulation.

After removing the goitre nodules (or nodule), together with the excessively hyperplastic tissue, the edges of the thyroid remnant (3-8 g), held by Billroth's clamps, are tied (or rarely sutured) with catgut. Several clamps are picked up and taken off at once. The tying of the catgut ligatures must be done very thoroughly. The catgut must be sufficiently strong; firmly tying the knot, it is necessary to fix the latter with one of the fingers so as not to tear away the remnant from the underlying tissues. The assistant must not lift the edges of the instrument to ease the placing of the ligature. When these conditions are not observed the soft tissues may be torn away and vessels ruptured, there may be a haemorrhage and blood boils, while improper technique of tying the knot may result in a subsequent slipping of the ligature and secondary haemorrhage. Therefore, in enucleating the goitre and removing it, the surgeon must always act very cautiously. When picking up and cutting the vessels their remnants must not be made too short. This ensures easy and convenient subsequent ligation of the vessels much farther from the location of the parathyroid glands and the recurrent nerve. When operating in conditions of complete haemostasis and good anaesthesia, choosing the most rational way for the least traumatic operation, depending on the anatomical features of the goitre, and preparing for the easiest performance of the subsequent stages of the operation, the surgeon is able to make a radical operation, preserving the quantity of tissue necessary for the normal function of the thyroid, its blood supply and innervation.

The part of the thyroid remaining after goitre enucleation or resection with enucleation is carefully stitched or shaped, connecting the cross ligatures in such a way that the entire damaged surface should be covered as much as

possible by fascial layers. But this, incidentally, is not obligatory, inasmuch as it is better that the discharge from the thyroid tissue should go into the wound and the dressing and should not be absorbed by the organism, causing a corresponding reaction. The main stage of the operation in one-sided nodular goitre ends with the shaping of the remnant. The remaining cavity of the wound is well delimited by the undamaged parietal layer of the fourth neck fascia. The thyroid remnant is covered by the sternothyroid muscle, after which the wound can be sutured and a small gauze tubing placed near the thyroid remnant. In two-sided goitre the same is done with the other side, carefully checking the condition of the unremoved part of .the thyroid so as not to leave separate nodules which could cause a relapse. Even in one-sided goitre the condition of the other thyroid lobe must be checked. In case small nodules are found in it, they should be removed and one-two knotty catgut sutures placed on the incised tissue. The thyroid isthmus, if it has no nodules, is preserved in part or in full, and the trachea usually remains covered with thyroid tissue.

In conclusion the cut muscles and other tissues are sutured and one or two drains are placed for 24 hours. The dressing protects the wound well. The dressing runs around the neck, under the armpits, covers the chest, crossing at the neck only in front. Patients, as a rule, can walk from the operating room themselves, but we would recommend to take them out in a wheel stretcher or wheel chair.

Thus, a goitre operation can be performed not only painlessly, but also without special trauma and loss of blood, with the patient feeling well.

The methods of operation vary in different forms of nodular endemic or sporadic goitre. Solitary nodules located in the middle, in normal or slightly enlarged lateral lobes are usually enucleated with a partial resection of the isthmus (also without ligating the thyroid arteries). In pro-

nounced hypothyroid phenomena the surgeon should strive not to remove slightly altered tissue, limiting himself merely to enucleation of the nodules with consecutive clamping of the vessels which feed the goitre. In intrathoracic goitres, rich in connective tissue which does not tear when using catgut "clamps", we at times use Hartert's method of drawing out the goitre with the help of many ligatures, with which we suture the goitre as it is dislocated. Intrathoracic goitre is also successfully operated under local anaesthesia. We know from literature that in some cases asphyxia from the compression of the trachea is possible in an operation of intrathoracic goitre. That is why it was recommended, when possible, to use the latest methods of intratracheal anaesthesia and in some cases also apparatuses for raising intrathoracic pressure. It should be noted that we have operated with full success both on partial and complete intrathoracic goitres without resorting to sternum incision or to general anaesthesia and did not employ special apparatus. We had to operate on intrathoracic goitres which descended 18 cm below the sternum incisure and reached the diaphragm arch. In relapsing goitres operations are more complicated.

After the operation patients remaining in a goitrogenous region should be prescribed constant prophylactic ingestion of iodine (1-2 mg potassium iodide weekly) or thyroidin (0.1 g weekly).

In non-radical methods of surgical intervention and the absence of postoperative iodine prophylaxis quite a large number of relapses was observed, reaching according to the data of some surgeons up to 40 per cent (I. A. Mityashin, Klose, Frizsche, and others). Modern methods, described above, give less than 3-4 per cent relapses, chiefly on account of conglomerate multinodular goitres; in cases of postoperative iodine prophylaxis (or systematic prophylactic ingestion of microdoses of thyroidin 0.05 g once or twice weekly) the percentage of relapses is even smaller.

To improve the results of operations some forms of sur-

gical intervention in endemic goitre should be abandoned. Strumectomy of the right or left lobe, i.e., the complete extirpation of the entire lobe of a thyroid with goitrous alterations, should in general lose their practical significance since these operations are not justified anatomically and physiologically. If we bear in mind that during the complete extirpation of a lateral lobe damage to the parathyroid glands and laryngeal nerve is highly probable and that ligation of the main trunks of the thyroid arteries is needed, the correctness of our thesis becomes perfectly clear. In hemistrumectomy the additional resection of the other lobe merely elevates the traumaticity and the nonphysiological nature of the operation, which also gives a large percentage of false relapses. This method has not withstood the test of time, and moreover, its direct postoperative results are unsatisfactory.

There is another reason why hemistrumectomy is inadvisable. Though technically it may seem more simple and safe from haemorrhage, actually ligation of both thyroid arteries may take up more time than the entire enucleation of the goitre which is made absolutely bloodlessly. We refer to the method of operation described above and not Socin's method, in which the goitre is enucleated by the finger without clamping beforehand the vessels entering it and, indeed, the haemorrhage not infrequently is catastrophic, notwithstanding the ligation of the main trunks of the thyroid arteries.

We also consider it necessary to concentrate attention on the irrationality of hemistrumectomy because this method is given undeservedly much space in some textbooks. A number of eminent surgeons, for example, V. A. Oppel, following Kocher, advocated this method, and now it has been revived by Y. S. Drachinskaya, who in thyrotoxic goitre recommends right-side total hemistrumectomy (together with removal of the isthmus and resection of the left lobe of the gland, of which only the upper pole is left).

Hemistrumectomy, i.e., extirpation of half of the gland, should be employed neither in "simple" (nodular goitre), nor in thyrotoxic goitre, except cases of one-sided malignant goitre when the diagnosis leaves no room for doubt or is well substantiated. In general, when operating for goitre the surgeon should always bear in mind the possibility of a number of operative and postoperative complications. In a properly performed operation for solitary nodular goitre, complications are almost ruled out, but in multinodular goitres complications may represent a substantial danger and occur even in the practice of experienced surgeons who mastered to perfection the technique of goitre operations.

Undoubtedly, chronic hypoparathyroidism is one of the gravest complications of this operation, a complication which turns a patient with goitre in a relatively satisfactory state into a very sick patient who constantly needs injections of parathyroidin and ingestion of calcium preparations. There are other possible grave complications of operations for simple goitre which give the surgeon many anxious minutes and days and demand much effort to save the life of the patients. Asphyxia during the operation might be caused not only by the compression of the trachea or its collapse, but also the reflectory spasm of the vocal cords in case of trauma or irritation of the recurrent nerve. Before the goitre is completely removed from the wound it is very difficult to arrest profuse haemorrhage as a result of the rupture of deep-seated blood vessels and for this reason not infrequently the surgeon has to ignore for some seconds the haemorrhage, being confident that after luxation of the goitre the blood vessel will be found and ligated.

Injury to the laryngeal nerve, besides aphonia and reflectory influences on the vocal cords and the heart (arrest!), creates conditions facilitating postoperative pneumonia, specifically aspirational.

Deep blood boils and suppuration are also dangerous because they may spread to the mediastinum if the surgeon ligates the inferior thyroid arteries at a distance, that is, behind the common carotid artery.

While in modern methods of subtotal resection of a thyrotoxic goitre injury to the recurrent nerve and the parathyroid glands is extremely rare, in operations for endemic goitre which do not involve such a large removal of thyroid tissue these complications are almost completely ruled out. In the other cases (asphyxia, haemorrhage, etc.) rational measures usually overcome the complications that arise.

Modern methods of operating on the thyroid, if they are properly mastered, preclude the possibility of air embolism. Nevertheless, in some conditions air embolism is possible.

A complication in the form of hypothyroidism might develop not only in cases of unjustified subtotal resection in endemic goitre or extirpation of the entire gland, but also in cases of a properly performed operation for an inveterate multinodular conglomerate goitre with big destructive changes. In some instances, when the surgeon cannot avoid removing too much of the altered tissues of the goitre which nevertheless possessed a certain hormonal function, he must reckon with the possible need of using thyroidin after the operation. Most often this is the case after operations for Riedel's or Hashimoto's strumas, in which hypothyroidism is at times inevitable even if no operation is made. That is why patients should be warned about the consequences of these diseases, otherwise they might be misled by physicians who are not familar with the nature of the goitre and attribute hypothyroidism to the operation itself. The importance of a microscopic study of the removed goitre is demonstrated specifically by the experience of M. N. Shevandin. A study of a goitre he resected revealed the presence of chronic thyroiditis (Riedel's struma) and it is not surprising that the prescription of thyroidin became necessary after the operation. In some

cases the administration of thyroidin also becomes necessary for patients who were given methylthiouracil in the preoperative period.

And so, when a surgeon undertakes to operate for goitre and decides on the method and scope of the operation, he should take into account not only the nature of the goitre, the local and general alterations caused by the latter, but also anamnestic data. Although experience suggests that definite general principles and most rational methods of operation, described earlier, have been elaborated in goitre surgery, nevertheless operations for goitre have their own distinctions and do not resemble each other. In fact, each case of goitre demands a special method of surgical intervention and, in the final count, it depends on the experience of the surgeon to choose the most rational one. It is important to strive for the utmost painlessness, minimal traumatisation of the tissue, most radical operation while limiting to the utmost the zone of surgical intervention, minimal loss of blood, careful ligation of the vessels and prevention of all dangerous complications possible in such operations. It must be particularly stressed that operations, even accompanied by the extensive removal of tissue of the goitrously degenerated thyroid, as a rule, do not result in the development of postoperative hypothyroidism.

As iodine prophylaxis is introduced and sanitary-hygienic conditions in goitrogenous regions improve, surgical treatment of goitre becomes limited primarily to operations eliminating the remnants of goitre endemy. This statement is fully corroborated by the results of the anti-goitre campaign in the Kabardino-Balkarian Republic where before the war the number of patients that had to undergo an operation declined steadily from year to year. The same is happening in a number of other regions of the Soviet Union. In general it should be stressed that the method of treating a patient with endemic goitre is determined by the form and duration of the disease, the functional disturbances, stage of the process, age of the patient, etc., i.e., the fullest

account and knowledge of the formal and causal genesis and also the aetiology of endemic goitre as a whole and the course of the disease in each particular case.

Surgical Treatment of Basedow's Disease (Thyrotoxicosis)

Surgical treatment of Basedow's disease (thyrotoxicosis) has registered particularly great successes in the last 20 or 30 years. In the present comprehensive medication of this disease an operation not infrequently culminates this treatment, while the conservative methods, used in the early stages as the main ones, become subsidiary and are employed in the preoperative preparation period, during the operation and partly in the postoperative period as well.

Surgical treatment of thyrotoxicosis has reached now such a high level that the question of indications for an operation is settled much easier than in the recent past. It has been greatly facilitated by the new conceptions regarding the course of this disease by stages (Milcu), and not only depending on the severity and age of the disease and the duration of conservative treatment. The question of indications for an operation has been revised in view of the development of preoperative preparation methods and lately, the elaboration of the problem of the so-called thymicolymphatic state and the ascertainment of the pathogenesis of this condition (O. V. Nikolayev). But a particularly great part in the successes of surgical treatment of thyrotoxicosis has been played by the development of modern methods of subtotal subfascial resection of the thyroid.

By dividing the course of thyrotoxicosis into stages of the process (after Milcu), namely, I—neurotic, II—neurohormonal (or endocrinal), III—visceropathic, IV—final, cachectic (marantic or dystrophic), we at once get a new basis for establishing indications for an operation. It is necessary only to recapitulate in brief the characteristic of these stages given in Chapter II to determine the indications for

an operation. The neurotic, I stage is difficult to differentiate from the state of vegetative neurosis with an elevated excitability of the nervous system, heart beat and tremor of the hands. In the II stage a diffuse enlargement of the thyroid is already noticeable, the symptoms of thyrotoxicosis grow stronger and more pronounced, the working capacity of the patient declines, exophthalmos often appears and the patients usually lose weight. In the III stage lesions of the internal organs and various systems (heart, liver, etc.) with disturbances and insufficiency of their function already develop. The IV stage is characterised by the conversion of the patients into gravely ill people with a pronounced general dystrophy or cachexia, disposition to auricular fibrillation, comatose condition and thyrotoxic storm from which they often die, just as from paralysis of a thyrotoxic dystrophic heart or accidental diseases (angina, grippe, etc.) or even slight intoxications.

It is clear from the above that to obtain the best results and avoid danger an operation should be made before the III stage of the disease sets in, i.e., in the II stage or the transition from the II to the III stage. In later stages the danger of an operation increases, but unfortunately in some cases the patient comes to the surgeon only when conservative medication dragged out impermissibly long, when the patient is in an extremely grave condition and a so-called "desperate operation" has to be performed. The latter is the only way of saving such patients since the use of I^{131} in such cases is even more dangerous than an operation as regards the possible exacerbation of the thyrotoxicosis, under whose influence visceral lesions increase and can lead to a lethal outcome. Even in such cases an operation usually saves the patient's life, but the results cannot be so indicative and, what is most important, even when thyrotoxic phenomena are removed, the lesions of the internal organs might prove to be stable and the condition of the patient might continue to remain grave. That is why when starting conservative medication, it is necessary

carefully to follow the results of treatment and the stage of the disease and, if the therapy does not prevent the onset of the III stage, it will be correct to suggest an operation.

Indications for an operation depend not so much on the period which passed since the disease began and the duration of conservative medication as on the form and course of the disease and the results of this treatment which not infrequently turns into preoperative preparation. If conservative treatment for 1.5-2 months in acute forms and for several months, at times even years, in other forms of the disease proves ineffective, surgical intervention is recommended. An operation is indicated not only in the III (and even more so, in the IV) stage, but often in the II stage of an acute form, especially if exophthalmos appears. When the condition of the patient grows worse in a chronic course of the disease, relative indications for an operation frequently appear already in the II stage. Consummating conservative treatment, an operation should be made prior to the development of pronounced lesions of the internal organs as a sequel of thyrotoxicosis, and not only in the final stage of the disease in the case of gravely ill patients. An operation is not indicated in mild thyrotoxicosis and in the initial stage of the disease when conservative treatment has not been fully tried out and when rapid improvement follows its application.

To make an operation it is necessary to choose the most favourable moment and to carry out definite preparatory measures (preoperative preparation). Thyrotoxic storms, sharp infectious ailments and a comatose condition represent temporary contraindications. Operations are performed successfully in case of tuberculosis or diabetes, provided these diseases are treated simultaneously. In pregnant women, when there are definite indications, an operation should be made and the pregnancy preserved. Patients with tonsillitis may be operated under the protection of antibiotics. If tonsillectomy is indicated and there is no

need for urgent strumectomy, tonsillectomy should come first.

Given the appropriate *preoperative preparation*, even patients in a serious condition may undergo surgical treatment. In 1924, Plummer proposed that patients be prepared for the operation by the ingestion of big doses of iodine (Lugol's solution 5-15 drops 3 times daily for 10-15 days). This method became widespread since in many cases the condition of the patients improved, they withstood the operation easier and such preparation reduced postoperative lethality. Preoperative treatment with iodine, as a rule, is given in clinical conditions.

Soviet surgeons use both microdoses (in pills) and also large doses of iodine. Many foreign surgeons also use large doses of iodine in Lugol's solution, often in combination with thiouracil preparations. Ganglioblocking and neuroplegic preparations have been introduced in recent years. They are especially indicated for patients with signs of psychic excitation and restless movement. Aminazine, aethyzine, dimedrole, at times hexonium and a number of other remedies are used a few days prior to the operation at first in the form of a trial dose and then, if the patient stands the preparation well, for 1-2 days prior to the operation, during the day of the operation and for 2-3 days after the operation.

Preoperative preparation must be individual, depending on the results of the all-round examination of the patient, the severity of the thyrotoxic phenomena and the alterations in the internal organs. Medicamentous, including hormonal, therapy should be combined with a corresponding diet, which calls for the intensive feeding of the patients. The mental influence on the patient exerted by the physician and the other medical personnel and also by patients recuperating after an operation is of great importance. The patient should be ensured the proper sleep regime and conditions promoting an elevation of the organism's compensatory possibilities. The length of the preparations and

the complex of methods employed depend on the stage, severity and nature of the thyrotoxic phenomena. The preoperative preparation in the clinic of patients in a serious condition, especially in the III and IV stages, is very important. In such cases, besides iodine (in microdoses), use is made of cortin (especially when there are symptoms of a thymicolymphatic state), small doses of insulin with glucose for emaciated patients and cardiants for patients with cardiovascular decompensation.

In particularly severe cases, besides preoperative preparation, the method of operation is of great importance. The method must ensure a radical, painless, brief and bloodless operation with minimal traumaticity. The methods proposed at the turn of the century did not meet these conditions adequately. After operations made at that time (and even now), when considerable quantities of thyroid tissue were left and the main thyroid blood vessels were ligated at a distance, more or less pronounced phenomena of postoperative thyrotoxicosis were observed. That is why prevention of postoperative thyrotoxicosis with the aid of preoperative preparations was considered of decisive importance in reducing postoperative lethality.

Preparation of patients with thyrotoxicosis for operation cannot be standardised; in any case the importance of iodine must not be overestimated. In this respect special attention should be paid not only to patients with severe forms and a prolonged course of thyrotoxicosis in the III and particularly IV stages who vainly underwent treatment with iodine, methylthiouracil and radioiodine, but also to patients with acute forms of the disease which as a rule are observed in the thymicolymphatic state. A special study of the literature on the *status thymicolymphaticus* has made it possible in the last ten years to change not only the previous conception that an operation is contraindicated for such patients, but also gave the surgeon a reliable method of preoperative preparation and postoperative treatment.

First of all, it was established that among patients with primary thyrotoxic diffuse goitre there is a special group of patients with the thyrotoxicosis developing against a background of the thymicolymphatic state. This state can be not only among primary (predominantly acute forms in young people), but also secondary (severe forms in adults) thyrotoxicosis. A study of this group of patients showed that the symptom complex of the thymicolymphatic state is combined with pronounced signs of adrenal cortex deficiency, which largely explains the inability of such patients to develop adaptive reactions in response to "stress" (intoxications, medical preparations, operation, wound, etc.). The correlations existing between the thymus and the adrenal cortex, established experimentally and clinically, explain the thymus enlargement in the thymicolymphatic state often encountered in thyrotoxicosis. This enlargement of the thymus can be observed even in emaciated patients in the visceropathic and final dystrophic stage of the disease.

Inasmuch as the decreased function of the adrenal cortex is an essential sign of the thymicolymphatic state in thyrotoxic patients, the use of adrenal cortex preparations in this group of patients (at times also the adrenocorticotropic hormone) bears the nature of directed influence on the development and course of the indicated adaptive reactions in response to the state of stress.

Surgical intervention in this group of patients must be preceded by especially thorough preparation; in particular, besides the comprehensive medicamentous treatment, attention should be paid to the diet of the patient and the establishment of personal contact of the patient with the surgeon (confidence in the success of the operation, the absence of fear, etc.). The operation must be of a maximally radical nature. In the postoperative period, besides adrenal cortex preparations, oxygen and glucose, there is need for intensive feeding and especially sedative, somnific and antipyretic (pyramidon and phenacetin) drugs. On the

other hand, narcotics (pantopon, morphine and even promedole) are contraindicated. The question of using neuroplegic drugs for this group of patients requires further study.

The principle of comprehensive medication dictates rational use of pathogenically substantiated therapy or corresponding means for each patient during the preoperative period. Everything must be done to reduce to a minimum the losses of energy which are observed during each operation and can be very considerable in thyrotoxicosis with an elevated level of metabolic processes, disturbances of assimilation-dissimilation processes accompanied by hypoxia, the loss of the stores of carbohydrates and proteins and disturbance of the normal acid-base equilibrium.

At times a stereotyped preoperative preparation with the standard use of iodine or methylthiouracil is absolutely ineffective, and in such cases it merely lengthens the stay of the patient in the clinic and delays his return to work. Often in a timely operation, i.e., in the II stage, good feeding of the patients for a few days and the use of somnifics is sufficient to prepare them for the operation.

We maintain that for the success of an operation the *method of operation* and the quality of its performance are of exceptional importance. Auxiliary measures merely facilitate this success.

We now go over to the methods of modern operation for Basedow's disease (primary thyrotoxic diffuse goitre).

Inasmuch as our method of operation has been developed as a result of summarising the entire experience of thyroid surgery and is a fundamental improvement over the old methods, a description of its main principles and separate details should be preceded by brief remarks on the history of surgical treatment of Basedow's disease.

We knew well that the introduction of iodine preoperative preparation, after Plummer, had sharply reduced postoperative lethality from an exacerbation of the thyrotoxicosis. A deeper study of the literature on this question

revealed that thyrotoxicosis declined especially in total extirpation of the thyroid after Sudeck. This operation for Basedow's disease did not become widespread and was abandoned as unjustified anatomically and physiologically. But observations of the results of operations after Sudeck were not utilised. These results showed that in a number of cases myxoedema did not develop after this operation. It was obvious that myxoedema did not arise because small remnants of thyroid tissue were left accidentally during the operation. Two conclusions should have been drawn from these observations.

First, during the full extirpation of the thyroid no postoperative thyrotoxicosis was seen even in seriously ill patients. Second, a small quantity of thyroid tissue, even if left accidentally during the operation, is sufficient for ensuring the incretory function of the gland within the physiologically necessary bounds. These two conclusions were laid at the basis of our method of subtotal resection of the thyroid.

A. V. Martynov already pointed out that excessive traumatisation of the thyroid increases postoperative thyrotoxicosis. From this we drew another important conclusion, namely, the least dangerous and best method of operation must be the one which leaves not only the minimal quantity of thyroid tissue the organism needs physiologically, but also preserves a normal innervation and blood supply for the thyroid remnant. From this point of view a one-stage operation without ligation of the thyroid arteries at a distance should have advantages over multi-stage operations accompanied by the ligation of three or four thyroid arteries.

It is known that ligation of four arteries, after Wölfler, even without resection of the thyroid tissue, at times results in a severe exacerbation of the thyrotoxicosis owing to tissue destruction.

Of the subsequent stages in improving the technique of thyroid operations, mention should be made of the positive

tendencies in Martynov's method. These operations were named subtotal thyroidectomy by the 8th International Congress of Surgeons in 1929.

Just as in our country in 1925, these operations were recommended in 1929 abroad (Crile and others) as the select method of operation for Basedow's disease (with ligation of the blood vessels at a distance).

We hold that a resection can be called subtotal only if a minimal quantity of thyroid tissue (not more than 2-6 g) is left. This demand is not met by operations proposed by a number of authors (Hertzler, Enderlen, Sauerbruch, Petenkofer, and others). The latest modification of Martynov's "subtotal" resection, which became more radical in the hands of P. G. Melikhov, is to remove two upper thirds of the thyroid and resect the lower third. Sections measuring 3×2×1 cm, each weighing 6-10 g, are left on each side. Consequently, altogether 12-20 g of tissue are left, not counting the tissue adhering to the remnants of the superior thyroid arteries.

Owing to unjustified apprehension of haemorrhage from the thyroid arteries, for a long time the use of silk ligature was considered obligatory and the use of catgut was out of the question. Nevertheless, Martynov's operation contained some progressive features—reduction of traumaticity and limitation of the zone of operative intervention. True, in many cases, as Melikhov wrote, it was impossible or very hard to make the continuous suture recommended by Martynov owing to the loss of elasticity by the thyroid tissue.

The operation recommended by Y. S. Drachinskaya is technically simpler. It calls for the complete extirpation of the thyroid, except the upper pole of the left lobe. Undoubtedly in this operation there is great danger of injury to the parathyroid glands and the recurrent nerves. That is why it cannot be regarded as substantiated anatomically. The only advantage of Drachinskaya's operation over Sudeck's method is that it leaves the quantity of thyroid

tissue physiologically needed by the organism. But, just as in the Sudeck operation, the parathyroid glands are endangered not only during the operation, but also in the process of wound healing because they may become involved in the cicatrising process.

Thus, the so-called "classical" and some new methods of operation for Basedow's disease, especially those that are usually described in contemporary text-books, should be abandoned. Most of them have big shortcomings, they result in a crude and unjustifiably big trauma and the opening up of deep cervical spaces connected with the mediastinum and with physiologically important organs. These operations create unfavourable conditions for the thyroid remnants, in which necrotic processes might easily arise. At the same time there is always the possibility of absorption of the wound discharge, rich in thyrotoxic products (owing to the wide opening of deep cervical spaces and the suction action of the thoracic cavity), which can sharply increase the thyrotoxic reaction. This danger rises especially in ligation of 3-4 thyroid arteries at a distance and the associated traumatisation of the nerve paths in the large wound zone. In such cases traumatisation of the vagus is also possible. Y. K. Molodaya was right when she drew special attention to the fact that irritation of the vagus by blood boils was often the cause of postoperative lethality of patients with Basedow's disease.

She noted that the use of our method excludes this danger because we fully discontinued the ligation of the thyroid arteries at a distance, thanks to which the region of the vascular-nerve bundle remains beyond the bounds of surgical intervention.

While raising the radical nature of the operation to the physiologically permissible bound, we preserve the anatomical relations of the remnant of the resected thyroid with the other important cervical organs (parathyroid glands, trachea).

Surgical treatment of the thyroid can hardly be called aetiological. An operation as such must be substantiated pathogenically, anatomically and physiologically. An operation in thyrotoxicosis is undertaken when the aetiological factor is left behind and a chain of new causes and consequences in the pathogenesis of thyrotoxicosis makes futile all kinds of conservative measures which, it would seem, should follow from the conceptions of the pathogenesis. But the operation itself, like a precise experiment, makes it possible not only to verify the correctness of the theoretical grounds of the chosen method, but also to make a number of observations which reveal the substance of thyrotoxicosis.

Observation of the mechanism of thyrotoxicosis and the results of surgical intervention convincingly demonstrate the correctness of, and need for, combating postoperative thyrotoxicosis as the main danger in the surgical treatment of these patients. Our efforts have been concentrated on preventing the development of postoperative thyrotoxicosis. We have accomplished this prophylactic task (beginning with 1932) by radically changing and improving the method of operation based on the pursuance of definite general principles. We shall first describe only the principles of subfascial subtotal resection according to our method.

1. *Minimal traumatisation of the tissues, specifically the thyroid tissues.* For this purpose we have limited the operation field to the 4th neck fascia (according to Shevkunenko, or the 3rd fascia, according to Pirogov) which covers the thyroid with a visceral layer and the adjacent muscles with a parietal layer. We have abandoned ligation of the main trunks of the thyroid arteries not only at a distance, but also at the point of entry into the thyroid gland, and ligate only the relatively smaller branches connected with the visceral layer of the 4th fascia and the branches of the vessels in the thyroid remnant. This rules out any possible injury to the parathyroid glands and the

laryngeal nerves. They, just like the cervical vascular-nerve bundle, remain outside the operation field, being covered by the remnants of the thyroid and the vessels and by the visceral fascia layer, pushed aside from the thyroid, which grows thicker in the posterior part. For the complete application of the first principle, besides exact knowledge of anatomy and ability to distinguish the tissues, the surgeon must be cautious in handling the tissues when isolating and luxating the thyroid and in effecting haemostasis. To facilitate the separation of the right lobe we, as a rule, incise the isthmus, separate the thyroid tissue from the trachea and release the right lobe, if possible, by drawing it out, and not by luxating it.

The small traumaticity of the operation has a favourable effect on the state of the patients who after the operation do not complain either of special fatigue or dizziness, and they usually feel well.

2. *The least possible loss of blood during the operation.* This is achieved by the consecutive placing of a considerable number of Billroth's clamps on the branches of the thyroid arteries and veins which pass and cover the visceral layer of the 4th fascia and the thyroid tissue left for shaping the remnant. We make the resection with an incised isthmus and often control it with a finger pushed under the gland; we press down the blood vessels with the finger, which also helps to make the operation bloodless. The subsequent ligation of the vessels, when shaping the remnant, is made with catgut ligatures. We usually group several instruments for ligating with one ligature: at times we use suturing to ensure haemostasis.

As a result, the most crucial stages of the operation, as a rule, pass in conditions of complete haemostasis. Special studies of the blood loss (M. I. Balakhovskaya) have shown that in the course of the entire operation patients, as a rule, lose not more than 25-50 g of blood. Consequently, an operation which had the reputation of one of the bloodiest, has become almost bloodless.

3. *Prophylaxis of postoperative thyrotoxicosis as the main danger.* In fact, all the principal demands made on the method of operation described above are subordinated to this aim. In properly performed subtotal resection there can be no thyrotoxicosis. This is shown by the decreased iodine content of the blood after a radical operation. A number of details of the operation is of especial importance. We achieve minimal absorption of thyrotoxic products from the wound by making a real subtotal resection since we leave not more than 1-3 g of tissue (in other methods, 6-10 g are left) from each thyroid lobe, depending on the degree of thyrotoxicosis, size of goitre, nature of the preceding treatment and other clinical data. In some cases of especially severe thyrotoxicosis and grave condition of the patient it is better to leave a minimal quantity of tissue and risk temporary hypothyroidism than to leave more tissue and lose the patient because of an exacerbation of the thyrotoxicosis. We have achieved a reduced thyrotoxic reaction by repeated washing of the wound with a novocain solution to remove mechanically the loose fragments of tissue and the gland juices and also by repeated novocain injections.

The possibility of absorption of the wound discharge containing thyrotoxic products is greatly reduced by the fact that the deep spaces of the neck which are filled with loose cellular tissue and are rich in lymphatic vessels remain outside the operation field. We refer to the region of the vascular-nerve bundle and the inferior thyroid artery intimately connected with the mediastinum. The absorption of the wound discharge is also reduced because the suction action of the thoracic cavity is not considerable in a wound with two gauze drains. These drains, just as the additional anaesthesia and washing of the wound with a novocain solution before stitching it up, ensure the maximum drainage of the wound discharge into the dressing.

Our method removes the tremendous danger of postoperative thyrotoxicosis or, as B. N. Mogilnitsky said, of a

thyrotoxic attack directed against the entire organism and the pathologically altered systems and organs. This is confirmed by a number of special studies (T. P. Bolotova) of the permeability of the capillaries and also data on the decrease of the iodine content of the blood after the operation (G. M. Gurevich).

Mogilnitsky's autopsy data convincingly demonstrate the great importance of lesions of the nervous system, central and peripheral, of the liver, kidney, heart, etc., in connection with the sharply disturbed vascular permeability during such a thyrotoxic attack. Studies with a luminescent microscope have shown that serum protein, albumen, accumulates in intercellular spaces, outside the cellular walls. The resultant hypoxemia and additional poisoning with metabolic products, in the opinion of Mogilnitsky, largely explain the dystrophic changes in the parenchymatous tissues and connective tissue elements, specifically in the argyrophil fibres.

There is no doubt that the size of the operation trauma and the quality of anaesthesia determine the degree of the shock reaction of the patient (to which Gurevich drew attention). An increase in the severity of the operation trauma and a postoperative thyrotoxic attack raise postoperative lethality. These and other causes of lethality may be removed by improving operation techniques and abandoning discredited ways characteristic of a number of obsolete methods.

4. *Improved anaesthesia.* The aim of anaesthesia should be not only to achieve complete painlessness, which from the very outset of the operation eliminates psychic excitation and ensures the calm state of the patient needed for the successful work of the surgeon, but also to reduce nerve reflectory influences. This is accomplished by a blockade of the thyroid interoceptors from the higher parts of the nervous system (in the first place, the cerebral cortex). Anaesthesia must reduce to a minimum the irritation of the reflexogenic zones of the operation field.

Infiltrational sheath anaesthesia of an 0.25-0.5 per cent novocain solution, made by stages, according to the method of A. V. Vishnevsky, fully conforms to these requirements. We have been using this method since 1930. We draw special attention to the harm of adding adrenalin to the novocain solution in thyrotoxicosis. The novocain infiltrate covers the thyroid and, spreading between the parietal and visceral layers of the 4th neck fascia, favourably changes the nerve reflectory mechanism of thyroxin action, in view of which the pulse rate is slowed down (often up to normal). Not infrequently, even tachyarrythmia disappears (for several hours or entirely). No shock phenomena during an operation according to our method are usually observed. This is explained by the fact that the operation is painless and that the entire field of surgical intervention is blocked by the novocain. The humoural connection of the thyroid with the entire organism is preserved; the quantity of the thyroid hormone circulating in the organism is the same and perhaps even larger, but its action on the tissues and organs, specifically, cardial activity, in conditions of the novocain blockade of the thyroid, is manifested not so sharply as prior to anaesthesia.

Consequently, the irradiation of excitation from the thyroid interoceptors, which are influenced by the specific products of the thyroid tissue, disappears in conditions of blockade of the thyroid. When the effect of anaesthesia passes and wound processes begin to act and the irritation, now coming already from the entire field of surgical intervention, changes the state of the nervous system and then again thyrotoxicosis is manifested, the pulse rate grows faster, although undoubtedly after the removal of the main mass of thyroid tissue the quantity of the hormone (iodine in the blood) becomes much smaller. In conditions of physical and medicamentous hibernation the metabolic processes are reduced owing to the lower temperature of the body; the action of the ganglioblocking means suppress the shock reaction.

5. *Proper posture of the patient on the operating table.* The patient is placed on his back, a firm pillow is put under his shoulder-blades; the head is thrown back, as a result of which the neck sharply protrudes forward. The patient must lie freely, without tensing his muscles, resting, and not getting tired. The sterile sheet which separates the small operation field is thrown over the arch in front of the patient's face and the edge of the duplicature is put under the chin. Thus, the patient's face, isolated from surgical action, can be well seen and the patient has an influx of fresh air. The operation field is prepared in the usual way and is treated with a tincture of iodine. In this position of the head the skin shifts upward, the goitre also moves upward, thanks to which the subsequent operation scar is in the lower part of the neck or even on the chest.

Subtotal resection of the thyroid, according to our method, performed with the object of curing thyrotoxicosis and preventing its exacerbation in the postoperative period, can rightly be called a pathogenetic method of treating Basedow's disease. The enumerated principles of our method have been developed, through constant improvement in the process of their elaboration. At present this method has become the most widespread in the Soviet Union and is being introduced in other countries as well.

The successes of surgical treatment, according to the method of subfascial subtotal resection of the thyroid without ligation of the main thyroid blood vessels, have made this method the principal one not only in severe thyrotoxicosis, but also in many cases of mild and moderately severe forms of this disease. According to data of a countrywide poll conducted by S. V. Semyonov (clinic of B. V. Petrovsky), subtotal subfascial resection, according to Nikolayev's method, has become very widespread in the Soviet Union. This method was used by 80 per cent of the surgeons who took part in the poll. The same picture was also revealed in reports at the 8th Congress of Surgeons of the Ukraine in 1954.

Technique of subtotal subfascial resection of the thyroid. A collar incision on the neck is made under local anaesthesia, administered according to the method of A. V. Vishnevsky. After cutting both sternohyoid muscles, novocain is introduced into the sheath of the 4th fascia around the thyroid. The sheath is incised along the central line and the subfascial separation of the thyroid begins more often with the cutting of the isthmus; in some cases it begins with separation of the upper pole of the right lobe and subsequent incision of the isthmus; the separation of the left lobe usually starts at the lower pole from the trachea. All the vascular branches in the visceral layer of the fascia, which is pushed back to the level of the resection, are gripped by Billroth's straight clamps. The separation of the thyroid lobes is made either by luxation with the finger or by drawing out the thyroid (which causes less of a trauma); in so doing the surgeon picks up all the vascular branches and cuts them in the layer of the fascia pushed back from the thyroid. Subtotal resection of the thyroid is made under the control of the finger. The vascular branches in the fascia and thyroid remnants are ligated with catgut.

Judging by the shape of the remnants the resection is sooner boat-shaped than wedge-shaped, inasmuch as the posterior-interior surface of both lobes is maximally preserved, representing small ovoid discs (2-3×1 cm), at times folded over in the shape of a duplicature when the vessels and tissues are ligated. The thyroid remnants, covering the "danger zone", where the parathyroid glands and laryngeal nerves are located, preserve normal innervation and blood supply, which is of great importance for maintaining their function, the prophylaxis of postoperative thyrotoxicosis and for preventing the danger of possible complications (paralysis of the vocal cords, tetany and myxoedema). After removing the firm pillow from under the patient's shoulder-blade, the thyroid remnants are covered with the sternohyoid muscles which are stitched up. The

wound which does not communicate with the deep neck spaces thanks to the fascial isolation, is washed with novocain. One or two thin gauze or rubber strips are inserted near the thyroid remnants and left for 24 hours. The subcutaneous cellular tissue and the skin are stitched up by layers with catgut (silk is not used in the operation).

After the wound is dressed the patient is put to bed in the usual position on his back with his jaw resting on the chest. Two or three pillows (without a firm pillow) are placed under his head and back. The patient must lie calmly, without tension, making at times respirational exercises (deep inhalations). On the day of the operation, both before and after it, the patient may have sweet tea, natural fruit juices, fruit jelly, broth and semi-liquid food. After the operation, if necessary, oxygen, pyramidon, somnifics, digitalis and glucose are administered. Usually the temperature rises slightly after the operation (very seldom above 38° C); after 8-12 hours the pulse rate temporarily increases. On the fifth or sixth day the stitches are removed and, following the direction of the drain, the wound is probed slightly to drain off the wound discharge. This is repeated in the subsequent three or four dressings until the wound heals. The patient is usually released from the hospital on the 8th-15th day. The operated patients are advised not to resume work for two or three weeks after the wound heals. Stay in a rest home or sanatorium is indicated for such patients (in summer, in the central zone).

Operations in relapses of Basedow's disease are harder to perform, but they are made according to the same principles of subfascial subtotal resection. The scars are clamped and cut like the visceral layer of the 4th fascia. In this way it is easier to operate, the danger of injury to the adjacent important cervical organs is reduced and complications are prevented.

Many foreign (for example, American) surgeons make subtotal resections of the thyroid without its subfascial isolation and with ligation of the superior or all the four

thyroid arteries at a distance. They usually employ a general (specifically, intratracheal) anaesthesia. Ligation of the arteries at a distance is also used by some Russian surgeons (Y. S. Drachinskaya, I. S. Zhorov, V. N. Shamov, V. S. Levit and others). Martynov usually operated under a general anaesthesia and the same is done now by Zhorov. Medicamentous hibernation is employed by foreign and some Soviet surgeons (B. V. Petrovsky, V. I. Kazansky, P. A. Kupriyanov, O. V. Nikolayev and others).

Russian statistics indicate a steady decline in postoperative lethality in subtotal thyroid resection and an improvement in postoperative results. Thus, according to statistics of I. A. Kadnikov (1914), of 1,608 operated patients, there was a full cure only in 30.4 per cent, an improvement in 55 per cent, no success in 5.1 per cent, while 9.5 per cent of the patients died. About the same time and in later years (between 1910 and 1925) postoperative mortality in 54 operated patients, seen by Martynov, was 5.8 per cent. Lethality declined after the introduction of preoperative preparation suggested by Plummer. After 1926, according to data of Martynov, it was 3.2 per cent for 256 operated patients. In the case of other surgeons it fluctuated from 3 to 8 per cent.

Improved methods of subtotal thyroid resection and of preoperative preparation have cut postoperative lethality to 1.7 per cent (data of V. S. Semyonov for the past 5-10 years, based on observations of 82 Soviet surgeons in 11,090 operations). The lethality figures of some surgeons are still lower. Thus, in the clinic headed by B. V. Petrovsky it was 1.6 per cent; A. T. Lidsky, 0.9 per cent; B. S. Rozanov, 1 per cent; A. V. Fedinets, 1 per cent: A. F. Lepukaln, 0.5 per cent; O. V. Nikolayev, 0.4 per cent. In recent years our figure declined to 0.2 per cent.

V. S. Semyonov polled 56 surgeons (heads of clinics) in Poland, Czechoslovakia, Hungary, Rumania, Bulgaria and China who reported the results of 16,999 operations. Postoperative lethality ranged from 0 to 9.6 per cent, averaging

1.5 per cent. According to data of K. Czarski (Bratislava), lethality in 1,640 operations averaged 1.9 per cent. R. K. Drewe (Poznan) observed lethality of 1.2 per cent in 538 operations. Similar results are also reported by other foreign surgeons who widely employ antithyroid substances for preoperative preparation and general anaesthesia (intratracheal and others).

Cattell reported the results of 1,000 operations between 1943 and 1949 in patients prepared with the aid of propylthiouracil in combination with iodine. Subtotal resection was made under ethylene-oxygen-ether anaesthesia (in most cases, intratracheal), with ligation of all the four arteries, isolation of the recurrent nerves and visual control of the parathyroid glands, leaving 3-4 g of tissue in each lobe. There were no postoperative thyrotoxic storms and lethality amounted to 0.24 per cent. Of complications there were haemorrhages (2.7 per cent), disturbance of the function of the vocal cords and collapse of the trachea which in 13 cases necessitated tracheotomy. Stable tetany was seen in 1.5 per cent of the patients and transitory tetany, in 1.5 per cent. Since the frequency of hypothyroidism rises when the preoperative preparation is made with antithyroid substances, 4.5 per cent of the patients had symptoms of hypothyroidism for several months, in view of which they had to ingest thyroid preparations. Notwithstanding the employment of the method described above, there were injuries of the recurrent nerves in 1 per cent of the patients.

According to data of Judd, still lower postoperative lethality was registered in the Mayo clinic (1943-1951): 0.2 per cent in 2,125 operations for Basedow's disease. Moreover, since 1946 there has not been a single death in 1,119 operations. According to data of Wienblad, between 1948 and 1953 lethality was 0.22 per cent for 1,817 operations in Stockholm hospitals. There was not a single death in the case of 1,000 patients with Basedow's disease when, in conformity with the indications, various surgical and conservative methods of treatment were used (operation

with ligation of the four thyroid arteries under local or general anaesthesia, radioiodine, antithyroid substances). According to data of Rosenquist, postoperative lethality in Sweden was 0.6 per cent in 1952, 2.3 per cent in 1942 and 4 per cent in 1932.

Notwithstanding the low postoperative lethality, the figures of Cattell, Weinblad and others show that the methods used (ligation of the four blood vessels) has essential shortcomings as compared with the Russian method, which conforms most to physiological principles. Weinblad reported paralysis of the recurrent nerves immediately after the operation in 7.5 per cent of the cases (which persisted after 3 years in 1.9 per cent of the patients), 3 per cent of concealed and 1.1 per cent of pronounced tetany and 7.7 per cent of hypothyroidism (including pronounced myxoedema); this can be explained not only by disturbance of blood supply and innervation of the thyroid remnants owing to the ligation of the vessels, but also by the earlier treatment with antithyroid substances, which reduced the function of the thyroid tissue. The same should be said about the above-mentioned complications (paralyses, tetany and asphyxia which required tracheotomy and others) in operations under general anaesthesia made in the Lahey clinic. All these complications are fully avoidable in operations made according to a method more substantiated not only anatomically but also physiologically.

Table 3 gives data, summarised by V. S. Semyonov, on the number of postoperative complications (percentage):

Table 3

Postoperative complications	Data of poll in the U.S.S.R.	Data of People's Democracies
Injury of the recurrent nerve	0.9*	1.5
Tetany	0.7*	1.1
Hypothyroidism	0.05	0.02

* According to data of O. V. Nikolayev (taking into account distant results in 1955), injury to the recurrent nerve and tetany were seen in less than 0.1 per cent.

Account of distant results shows that an operation rids the patient not only of thyrotoxicosis, but also of many consequences of this disease. Only some patients who are operated too late continue to make complaints and remain sick, notwithstanding the complete remission of thyrotoxicosis. It should be noted that in severe forms of the disease distant results of surgical intervention are much better than in other methods of treatment. In milder forms of the disease an operation is especially effective. On the basis of a study of 12,960 people operated prior to 1932, Crile established that 97 per cent became practically healthy and that 86 per cent of the patients resumed their normal occupations. According to data of V. S. Semyonov, Soviet surgeons on the average observe recovery of 88.7 per cent of the operated patients and 3.7 per cent of relapses. O. V. Nikolayev reported 0.3 per cent of relapses, pointing out that if the operation is performed in time recovery in 100 per cent of the patients can be attained. Surgeons in the People's Democracies also report 89-100 per cent of favourable results, with relapses averaging 1.2 per cent (ranging from 0.2 to 10.6 per cent).

To prevent relapses the operation has to be of a radical nature and conditions have to be created which preclude the influence of psychic traumas and ensure a proper regimen of work and rest. At present there is a correct tendency when conservative treatment proves ineffective to broaden the indications for an operation at an early stage of Basedow's disease, before irreversible changes develop in the patient's organism.

A study of distant results of surgical treatment of thyrotoxicosis, made by us before the Great Patriotic War of 1941-1945, showed that Basedow's disease is cured in 98-99 per cent of the patients. At present the results should be evaluated depending on the stage of the disease in which the operation is performed. Timely surgical treatment ensures the full cure of the

patients and complete restoration of their working capacity.

The outstanding successes in the surgical treatment of thyrotoxicosis are a result of the cumulative experience in the study and medication of this disease. It is this that led us to the development of the contemporary Soviet method of subtotal subfascial resection of the thyroid which proved to be the most effective.

TO THE READER

The Foreign Languages Publishing House would be glad to have your opinion of the translation and the design of this book.

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